CEFTAZIDIME-AVIBACTAM FOR INJECTION

for

Treatment of Complicated Intra-abdominal Infection (used in combination with metronidazole), Complicated Urinary Tract Infection including Acute Pyelonephritis, and Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options

NDA 206494

Briefing Document

Anti-Infective Drugs Advisory Committee

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AEoSI	adverse event of special interest
AERS	Adverse Event Reporting System
ALT	alanine aminotransferase
AmpC	Ambler Class C
APACHE	Acute Physiology, Age, Chronic Health Evaluation
ARC	augmented renal clearance
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0\text{-}tau}$	area under the plasma concentration-time curve from time 0 to time t corresponding to the last measurable concentration
BAT	best available therapy
BL-BLI	β-lactam β-lactamase inhibitor
BLI	β-lactamase inhibitor
CAZ-AVI	ceftazidime-avibactam
CAZ-AVI + MTZ	ceftazidime-avibactam plus metronidazole
CAZ-I	ceftazidime-intermediate
CAZ-NS	ceftazidime-nonsusceptible
CAZ-R	ceftazidime-resistant
CAZ-S	ceftazidime-susceptible
CDAD	*Clostridium difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CFU	colony-forming unit
CI	confidence interval
cIAI	complicated intra-abdominal infection
CL	apparent total body clearance of drug from plasma
CLSI	Clinical Laboratory Standards Institute
C_{max}	maximum plasma drug concentration
CrCL	creatinine clearance
CRE	carbapenem-resistant *Enterobacteriaceae*
CSF	cerebrospinal fluid
C_T	threshold concentration
cUTI	complicated urinary tract infection
CXL	ceftaroline fosamil-avibactam
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
ED_{50}	median effective dose
ELF	epithelial lining fluid
EOIV	End of Intravenous Therapy
EOT	End of Therapy

ESBL	extended-spectrum β-lactamase
ESRD	end-stage renal disease
*f*T > MIC	duration of time a free or unbound drug concentration remains above the minimum inhibitory concentration
%*f*T > C_T	percent of time that free drug concentrations are above the threshold concentration over a dose interval
%*f*T > MIC	percent of time that free drug concentrations are above the minimum inhibitory concentration over a dose interval
FDA	United States Food and Drug Administration
HABP	hospital-acquired bacterial pneumonia
IND	Investigational New Drug
IV	intravenous, intravenously
KPC	*Klebsiella pneumoniae* carbapenemase
LFU	Late Follow-up
MDR	multidrug-resistant
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC_{90}	minimum concentration required to inhibit the growth of 90% of organisms
mMITT	microbiological modified intent-to-treat
MRHD	maximum recommended human dose
MRSA	methicillin-resistant *Staphylococcus aureus*
MTZ	metronidazole
NCSE	nonconvulsive status epilepticus
NDA	New Drug Application
OAT	organic anion transporter
PBP	penicillin-binding proteins
PCS	potentially clinically significant
PD	pharmacodynamics
PD_{50}	median protective dose
PK	pharmacokinetic
PTA	probability of PK/PD target attainment
QIDP	Qualified Infectious Disease Product
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected by the Fridericia formula
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SmPC	summary of product characteristics
$T_{½}$	terminal elimination half-life

TEAE	treatment-emergent adverse events
T_{max}	time of maximum plasma concentration
TOC	Test-of-Cure
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
VABP	ventilator-associated bacterial pneumonia
V_1	plasma compartment
V_{ss}	mean volume of distribution at steady state
WBC	white blood cell

1.0 EXECUTIVE SUMMARY

Ceftazidime-avibactam (CAZ-AVI) is a combination of a well-established β-lactam (ceftazidime) with a novel β-lactamase inhibitor (avibactam). This β-lactam-β-lactamase inhibitor (BL-BLI) combination is being developed to meet current and future critical unmet needs in the treatment of serious infections caused by resistant Gram-negative pathogens (Section 1.1). In the context of this unmet need, a new drug application (NDA) was submitted, which relies on historical efficacy of ceftazidime alone, pharmacokinetic/pharmacodynamic (PK/PD) analyses, in vitro microbiological studies, in vivo animal models, Phase 1 clinical pharmacology data, Phase 2 randomized clinical efficacy data, and initial Phase 3 data from a study of subjects infected with ceftazidime-resistant (CAZ-R) pathogens. This approach allows for the approval of CAZ-AVI for serious infections in which there are limited treatment options.

1.1 URGENT MEDICAL NEEDS IN RESISTANT GRAM-NEGATIVE INFECTIONS

In the context of the global bacterial resistance crisis, the United States (US) Centers for Disease Control and Prevention (CDC) has identified Gram-negative pathogens as particularly worrisome because they are becoming resistant to nearly all antibiotics that are routinely considered for treatment (CDC, 2013). The most serious Gram-negative infections include complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI), as well as serious nosocomial infections (eg, hospital-acquired bacterial pneumonia [HABP] and ventilator-associated bacterial pneumonia [VABP]), and the most common pathogens encountered in clinical practice include members of the *Enterobacteriaceae* family (eg, *Escherichia coli* and *Klebsiella pneumoniae*) and the non-fermenting Gram-negative bacilli (eg, *Pseudomonas aeruginosa*). Treating infections caused by pan-resistant or nearly pan-resistant Gram-negative pathogens is an increasingly common challenge in many hospitals.

The β-lactams are the main antibiotic class utilized as front-line therapy for serious Gram-negative infections (CDC, 2013); however, their use is being compromised by the emergence and spread of pathogens that produce β-lactamase enzymes, which hydrolyze the β-lactam ring of members of the class and render these antibiotics inactive. Hundreds of β-lactamases have been described, and they are classified into 4 molecular classes (Ambler Class A through D) (Jacoby and Munoz-Price, 2005). Class A and Class C β-lactamases are the most common and have a serine residue at the active site, as do the less common Class D β-lactamases. Class B comprises the metallo-β-lactamases, which contain zinc at the active site. Over the last 20 years, Gram-negative bacteria have evolved in defense against recently approved broad-spectrum β-lactam agents (eg, BL-BLIs and carbapenems) by producing a multitude of "new" β-lactamases across all Ambler classes—including extended-spectrum β-lactamases (ESBLs) and carbapenemases—that can confer resistance to these front-line agents (Jacoby and Munoz-Price, 2005). In the context of these emergent β-lactamases in Gram-negative pathogens, 4 distinct medical needs for new effective antibiotics have been identified (Table 1).

CAZ-AVI addresses important needs in the treatment of Gram-negative infections, including those caused by ESBL-producing Gram-negative pathogens, carbapenem-resistant *Enterobacteriaceae* (CRE), and multidrug-resistant (MDR) *P. aeruginosa* (Table 1). Specifically, CAZ-AVI would provide clinicians with a new treatment choice for infections caused by CRE and a non-carbapenem option for ESBL-producers and MDR *P. aeruginosa*. Avibactam extends the activity of ceftazidime and provides the broadest spectrum of β-lactamase activity compared with currently available BLIs. Although limited clinical data are available for CAZ-AVI, the totality of evidence described herein supports CAZ-AVI as an effective and well-tolerated therapy against highly resistant Gram-negative pathogens.

Table 1. Unmet Medical Needs in Gram-negative Bacterial Infections

Gram-negative Pathogens	CDC Threat Level[1]	Scope of Medical Need	CAZ-AVI Activity
ESBL-producers	Serious	Of an estimated 140,000 healthcare-associated *Enterobacteriaceae* infections annually in US, 26,000 (18.6%) infections and 1,700 deaths attributed to ESBLs.[1] ESBL-producing *E. coli* or *K. pneumoniae* have been associated with a 1.9-fold greater risk of mortality, 1.8-fold longer length of hospital stay, and 2.9-fold higher median hospitalization cost compared with non-ESBL-producers[2] Carbapenems are therapy of choice; however, may be associated with toxicity-limiting adverse events (eg, seizures, hypersensitivity), and broad use may hasten the appearance of CRE and carbapenem-resistant *P. aeruginosa* or *Acinetobacter*; carbapenem-sparing options needed	Yes
CRE	Urgent	Of an estimated 140,000 healthcare-associated *Enterobacteriaceae* infections annually in US, approximately 9,300 (6.6%) are caused by CRE.[1] Carbapenem-resistant *K. pneumoniae* accounts for approximately 7,900 infections and 520 deaths, and carbapenem-resistant *E. coli* accounts for 1,400 infections and 90 deaths. CRE associated with 2-fold higher mortality than carbapenem-susceptible isolates[3] Sporadic outbreaks occur globally, including US[4] Extremely limited treatment options, eg, colistin (associated with toxicity and lack of supportive data to guide dosing)[5]	Yes
MDR P. aeruginosa	Serious	Of an estimated 51,000 healthcare-associated *P. aeruginosa* infections annually in US, more than 6,000 (13%) infections and approximately 400 deaths are attributed to MDR strains[1] Over 2-fold increased risk of mortality with MDR compared to susceptible *P. aeruginosa*, as well as increased hospital length of stay and cost burden[6]	Potential
Metallo-β-lactamase-producers	Not assessed	Currently rare; for example, approximately 60 cases of NDM-1 infection detected worldwide between 2008-2011[7] Extremely limited treatment options, eg, colistin (associated with toxicity and lack of supportive data to guide dosing)	No

Abbreviations: CRE = carbapenem-resistant *Enterobacteriaceae*; ESBL = extended-spectrum β-lactamase; MDR = multidrug-resistant; NDM-1 = New Delhi metallo-β-lactamase type 1.
[1] CDC, 2013; [2] Lautenbach et al, 2001; [3] Falagas et al, 2014; [4] Snitkin et al, 2012; [5] Boucher et al, 2009; [6] Nathwani et al, 2014; [7] Bushnell et al, 2013

1.2 REGULATORY PATHWAY

In March 2013, the Food and Drug Administration (FDA) granted the Qualified Infectious Disease Product (QIDP) and Fast Track designations for CAZ-AVI for the indications of cIAI, cUTI, and HABP/VABP. In the context of urgent unmet medical needs for antibiotics in the treatment of MDR Gram-negative bacterial infections (Section 1.1) and new regulatory pathway options described recently by the FDA (FDA, 2013), a revised development strategy was agreed upon to allow for approval of CAZ-AVI prior to the availability of Phase 3 clinical study data. Discussions between the Sponsor and FDA resulted in changes to the development plan after the initiation of the Phase 3 studies, including a streamlined Phase 3 program (ie, a single study per indication) and support for submission of a 505(b)(2) NDA (Section 1.2.1). At the Type B pre-NDA meeting held in December 2013, the FDA advised that PK/PD analyses, Phase 1 data and animal data and Phase 2 clinical data could support approval for CAZ-AVI via a 505(b)(2) NDA, which allows the efficacy and safety of CAZ-AVI to rely in part on the Agency's prior findings for the efficacy and safety of ceftazidime alone.

High-level safety data from two ongoing, blinded Phase 3 studies—one in cIAI and one in cUTI—are included in this NDA (Section 5.2); however, unblinded safety data from three ongoing Phase 1 Clinical Pharmacology studies and unblinded safety and efficacy data from the ongoing Phase 3 studies (cIAI, cUTI, and HABP/VABP) are *not* included in the submission. Final data for these ongoing Phase 3 studies will be reported in a supplemental NDA at a later date (Section 2.2).

Data in the CAZ-AVI NDA that satisfy the 505(b)(2) regulation (described in 21 CFR 314.54 and the FDA *Draft Guidance for Industry - Applications Covered by Section 505(b)(2)* [FDA, 1999]) include:

- Reliance on Agency's findings of safety and effectiveness of ceftazidime (ie, NDA N050578 and FORTAZ® Prescribing Information [FORTAZ package insert, 2010])
- Specific published literature necessary for the approval of a 505(b)(2) NDA, including a literature review and meta-analysis to determine the historical efficacy (Section 3.0) and safety (Section 1.3.4.2) of ceftazidime
- Appropriate bridging studies that provide an adequate basis for reliance upon the FDA's findings of safety and effectiveness of ceftazidime

The CAZ-AVI data presented here fulfill the above requirements of the 505(b)(2) NDA.

1.2.1 Proposed Indications for CAZ-AVI

Given the serious unmet need for new treatments for MDR Gram-negative pathogens, the totality of the data (as outlined above and including the data for ceftazidime alone as part of the 505(b)(2) regulatory pathway) adequately demonstrates that CAZ-AVI, administered by a 2-h intravenous (IV) infusion at a dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) every 8 h (q8h) is effective for the treatment of serious bacterial infections that are susceptible to CAZ-AVI—including those caused by ceftazidime-nonsusceptible (CAZ-NS) pathogens—supporting approval in the following proposed indications for patients in whom there are limited treatment options:

- Complicated intra-abdominal infections, in combination with metronidazole (MTZ), caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Enterobacter cloacae*, *K. oxytoca*, *Pseudomonas aeruginosa*, and *P. stutzeri*; and polymicrobial infections caused by aerobic and anaerobic organisms including *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant to CAZ-AVI).

- Complicated urinary tract infections, including acute pyelonephritis, caused by *E. coli* (including cases with concurrent bacteremia), *K. pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *E. cloacae*, *Citrobacter freundii*, *Proteus* spp. (including *P. mirabilis* and indole-positive *Proteus),* and *P. aeruginosa*.

- Aerobic Gram-negative infections with limited treatment options: CAZ-AVI may be used for HABP/VABP, and bacteremia where limited or no alternative therapies are available and the infection is caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. aeruginosa*, *P. stutzeri*, *P. stuartii*, *C. freundii*, *C. koseri*, *Serratia* spp., *E. aerogenes*, *E. cloacae*, and *Proteus* spp., including *P. mirabilis* and indole-positive *Proteus*.

Approval of CAZ-AVI in aerobic Gram-negative infections with limited treatment options in indications other than cIAI and cUTI (such as bacteremia and HABP/VABP) is based on clinical experience with ceftazidime alone, observed similarities between the PK properties of ceftazidime and avibactam, the efficacy of CAZ-AVI in animal models of bacteremia and pneumonia using CAZ-NS bacterial pathogens, and additional PK data demonstrating lung tissue penetration of avibactam.

The approval of CAZ-AVI for the above indications will provide clinicians with a new treatment option for serious bacterial infections, including those caused by MDR Gram-negative pathogens, while maintaining a similar safety profile to the established 3rd-generation cephalosporin, ceftazidime.

1.3 TOTALITY OF DATA SUPPORTING CAZ-AVI FOR UNMET NEEDS

The totality of data derived from the CAZ-AVI development program meet the requirements of the FDA Guidance Document entitled *Streamlined Antibacterial Drug Development Programs Targeting Unmet Need* (FDA, Jul 2014), based on the following:

- Ceftazidime alone has a 30-year history of efficacy against susceptible bacterial pathogens (Section 3.0)
- Combination of a BL-BLI is a proven strategy for overcoming Gram-negative bacterial resistance due to β-lactamase production (Section 4.1)
- Avibactam is a novel BLI with the broadest spectrum of β-lactamase activity compared with currently available BLIs (Section 4.1)
- Avibactam, when administered in combination with ceftazidime, extends the activity of ceftazidime against ceftazidime-nonsusceptible (CAZ-NS) pathogens, based on:
    - In vitro microbiological surveillance data from a large number of clinically relevant pathogens (Section 4.1.1)
    - In vivo animal models of infection including pyelonephritis, pneumonia, septicemia, and meningitis (Section 4.2.1)
    - Joint probability target attainment analyses for ceftazidime and avibactam based on PK and PK/PD data for each component alone and for CAZ-AVI (Sections 4.3 and 4.4)
    - Descriptive efficacy and safety data from two completed Phase 2 studies in hospitalized adults with cIAI and cUTI caused by ceftazidime-susceptible (CAZ-S) and CAZ-NS pathogens (Section 4.5)
    - Descriptive comparative efficacy and safety data from an ongoing Resistant Pathogen study in hospitalized adults with cIAI and cUTI caused by CAZ-NS pathogens (Section 4.5.3)
- Avibactam does not alter the safety profile of ceftazidime (Section 5.0)

These data show that CAZ-AVI provides a positive benefit:risk ratio for the treatment of cIAI, cUTI, and other serious infections caused by MDR Gram-negative pathogens for which there are limited treatment options (Section 6.0).

1.3.1 History of Ceftazidime Efficacy and Rationale for CAZ-AVI

Ceftazidime was approved in the US in July 1985 and is currently indicated for lower respiratory tract infections, skin and skin structure infections, urinary tract infections (both uncomplicated and complicated), bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections, and central nervous system infections. Ceftazidime has a well-characterized mode of action with its bactericidal activity being mediated by inhibition of penicillin-binding proteins (PBPs), which are important for the cross-linking of peptidoglycan in the bacterial cell wall. It exhibits broad-spectrum activity against clinically important *Enterobacteriaceae* and *P. aeruginosa* and has been an important agent for treating infections caused by common enteric Gram-negative pathogens. Its clinical efficacy and safety profiles have been well established over the past 3 decades (FORTAZ package insert, 2010). Ceftazidime is among agents recommended in guidance documents for the empiric treatment of cIAI (in combination with MTZ; Solomkin et al, 2010) and cUTI (Gupta et al, 2011).

The current NDA relies in part on prior efficacy and safety findings for ceftazidime. In this regard, a meta-analysis of the historical efficacy of ceftazidime was performed as part of the support for a 505(b)(2) submission. Results from this meta-analysis are presented in Section 3.0 and indicate that ceftazidime remains an effective antibiotic against CAZ-S pathogens.

1.3.2 Microbiology, Clinical Pharmacology, and Pharmacokinetics/Pharmacodynamics of CAZ-AVI

1.3.2.1 Avibactam and CAZ-AVI Characteristics

1.3.2.1.1 In Vitro Activity of Avibactam and CAZ-AVI

Avibactam is a first-in-class non-β-lactam, β-lactamase inhibitor with a broader spectrum of activity than currently approved inhibitors, including activity against Class A (including serine carbapenemases such as *Klebsiella pneumonia*e carbapenemases [KPCs]), Ambler Class C (AmpC cephalosporinases), and some Class D (eg, OXA-48) β-lactamase-producing organisms. Avibactam alone has no meaningful antibacterial activity and exhibits a unique mode of action that is driven by covalent, but reversible, inhibition of the β-lactamase enzyme resulting in the generation of active avibactam via a reverse deacylation reaction rather than hydrolysis to an open ring form. Avibactam also has no propensity for the induction of AmpC β-lactamases at clinically relevant concentrations.

In vitro profiling studies have shown that avibactam does not compromise the antibacterial activity of ceftazidime against either CAZ-S Gram-negative organisms or against Gram-positive pathogens. In contrast, avibactam extends the antibacterial activity of ceftazidime against well-characterized β-lactamase-producing strains of *Enterobacteriaceae* and *P. aeruginosa* as well as contemporary β-lactamase-producing organisms collected in a 2012 US surveillance program (Table 2). For all clinically important members of the *Enterobacteriaceae* and *P. aeruginosa*, the minimum inhibitory concentrations (MIC) required to inhibit growth of 90% of organisms (MIC_{90}) for CAZ-AVI were equal to or less than the current Clinical Laboratory Standards Institute (CLSI) and FDA interpretive criteria for ceftazidime (≤ 4 mg/L for *Enterobacteriaceae* and ≤ 8 mg/L for *P. aeruginosa*).

Table 2. Activity of CAZ-AVI and Comparators against US Gram-negative Pathogens from 2012 US Surveillance

Organism	***Phenotype***	***N***	***MIC_{90} (% Susceptible)[b]***			
			CAZ-AVI	***Ceftazidime***	***Meropenem***	***Piperacillin/ tazobactam***
E. coli	All	2767	0.12 (NA)	2 (91.8)	0.06 (99.9)	8 (95.2)
	ESBL[a]	328	0.25 (NA)	>32 (30.8)	≤0.06 (98.8)	>64 (76.8)
K. pneumoniae	All	1847	0.5 (NA)	32 (85.4)	≤0.06 (93.8)	>64 (86.6)
	ESBL[a]	296	1 (NA)	>32 (8.8)	>8 (61.1)	>64 (24.7)
	MER-NS[b]	115	2 (NA)	>32 (0.0)	>8 (0.0)	>64 (0.0)
E. aerogenes	All	357	0.25 (NA)	32 (77.0)	≤0.06 (99.4)	64 (80.6)
	CAZ-NS[b]	82	0.5 (NA)	>32 (0.0)	0.12 (97.6)	>64 (22.0)
E. cloacae	All	951	0.5 (NA)	>32 (79.0)	≤0.06 (99.5)	64 (85.0)
	CAZ-NS[b]	200	1 (NA)	>32 (0.0)	0.25 (97.5)	>64 (97.5)
P. mirabilis	All	683	0.06 (NA)	0.12 (99.1)	0.12 (100.0)	1 (99.7)
Citrobacter spp.	All	371	0.25 (NA)	16 (87.6)	≤0.06 (98.9)	16 (90.2)
	CAZ-NS[b]	46	1 (NA)	>32 (0.0)	1 (91.3)	>64 (32.6)
Providencia spp.	All	268	0.5 (NA)	4 (90.7)	0.12 (9.2)	8 (94.4)
P. aeruginosa	All	1967	4 (NA)	32 (83.2)	8 (82.0)	>64 (78.3)
	CAZ-NS[b]	330	16 (NA)	>32 (0.0)	>8 (45.3)	>64 (4.5)
	MER-NS[b]	354	16 (NA)	>32 (49.2)	>8 (0.0)	>64 (36.4)

NA = Not applicable, as there are no established breakpoints for CAZ-AVI.

a Defined as MIC > 1 mcg/mL for aztreonam and/or ceftazidime and/or ceftriaxone.

b Criteria as published by the CLSI M100-S24, 2014.

No cross-resistance with other classes of antimicrobial agents has been identified. In vitro studies have not demonstrated any antagonism between CAZ-AVI and colistin, levofloxacin, linezolid, MTZ, tigecycline, tobramycin, or vancomycin.

1.3.2.1.2 CAZ-AVI Resistance Potential

Spontaneous mutation frequencies were $\leq 10^{-9}$ at 4-fold the MIC. Spontaneous mutation frequencies of 2.2 x 10^{-8} to 10^{-9} at 4 x MIC were observed for KPC-producing organisms but were reduced at higher multiples of the MIC (Livermore et al., 2012), including MICs of 8 mg/L of CAZ-AVI (the proposed PK/PD breakpoint). Increasing the concentration of avibactam in single step resistance development studies further reduced the propensity for resistance development for organisms expressing KPC-carbapenemases. Furthermore, no resistant mutants were identified in any animal efficacy models with resistant pathogens when CAZ-AVI was tested as a 4:1 ratio or with simulated human exposures of 2.5 g CAZ-AVI (2 g ceftazidime + 0.5 g avibactam) q8h with a 2-h infusion. In the clinical trials, none of the isolates from CAZ-AVI-treated subjects that persisted at the Test-of-Cure (TOC) and Late Follow-up (LFU) visits showed resistance development as evidenced by > 4-fold increase in MIC from baseline.

1.3.2.2 CAZ-AVI In Vivo Efficacy in Animals

CAZ-AVI has demonstrated efficacy in several experimental animal infection models against β-lactamase-producing pathogens that were resistant to ceftazidime alone (Table 3).

Table 3. CAZ-AVI Animal Infection Models Studied with CAZ-NS Pathogens

Infection Model and Species Tested
Mouse peritoneal sepsis (PD_{50}) against *K. pneumoniae*, *E. cloacae*, *C. freundii*, and *E. coli*
Mouse thigh infection (ED_{50}) against *K. pneumoniae*
Mouse pneumonia (ED_{50}) against *K. pneumoniae*
Mouse pyelonephritis (efficacy) against *E. coli, C. freundii*, *K. pneumoniae*, *E. cloacae*, and *M. morganii*
Rabbit meningitis (efficacy) against *K. pneumoniae*
Mouse thigh infection (dose fractionation) against *P. aeruginosa*
Mouse lung infection (dose fractionation) against *P. aeruginosa*
Mouse thigh infection (simulated human PK) against *P. aeruginosa*
Mouse pneumonia (simulated human PK) against *P. aeruginosa*
Mouse thigh infection (simulated human dosing) against *S. marcescens, K. pneumoniae, E cloacae, E. aerogenes, K. oxytoca,* and *P. stuartii*

ED_{50} = median effective dose; PD_{50} = median protective dose.

CAZ-AVI demonstrated efficacy against selected ESBL and AmpC β-lactamase-producing *Enterobacteriaceae* in a murine kidney infection model by reducing the bacterial load in the kidney by 2 to 4 $\log_{10}$ colony-forming units (CFU) at 48 h post infection. In contrast, for animals treated with ceftazidime alone, the bacterial load was similar to the control after 48 h. CAZ-AVI was also efficacious against KPC-producing *K. pneumoniae* in a murine septicemia model. Animal survival increased significantly when ceftazidime was combined with avibactam showing that avibactam dramatically reduced the amount of ceftazidime required to favorably treat systemic infections induced in mice. In addition, mouse thigh and lung infection models using dosing to simulate plasma concentrations in humans for the proposed clinical dose demonstrated robust efficacy against challenging, and clinically important, CAZ-NS pathogens. Many of these challenging pathogens produced clinically-important Class A and C β-lactamases such as ESBL, KPC, and AmpC.

In summary, the robust preclinical microbiology program demonstrated the ability of avibactam to extend the in vitro antibacterial and bactericidal activity of ceftazidime against contemporary β-lactamase-producing Gram-negative pathogens such as *Enterobacteriaceae* and *P. aeruginosa*. Robust efficacy against multiple β-lactamase-producing organisms has been demonstrated in experimental animal infection models using CAZ-AVI either as a 4:1 ratio or with simulated human exposures. The results from animal models were predictive of the efficacy that was observed for CAZ-AVI against CAZ-NS pathogens in the Phase 2 cUTI and cIAI trials as well as the ongoing Resistant Pathogen study.

1.3.2.3 CAZ-AVI Clinical Pharmacology

As part of the CAZ-AVI development program, the PK of avibactam has been investigated in 10 Phase 1 Clinical Pharmacology studies after administration of avibactam alone or CAZ-AVI by IV infusion. Ceftazidime PK data were available from 7 of these Phase 1 studies as well as from the literature. Additional PK data for avibactam were provided by 4 Phase 1 studies from the ceftaroline fosamil-avibactam (CXL) program, and sparse PK samples were collected from the Phase 2 CAZ-AVI studies in cIAI and cUTI.

The PKs of ceftazidime and avibactam are linear, with maximum plasma drug concentration (C_{max}) and exposure (area under the plasma concentration curve [AUC]) increasing in proportion to dose. Both avibactam and ceftazidime undergo limited metabolism and there is no evidence of a drug-drug interaction (DDI) between ceftazidime and avibactam. No appreciable accumulation of ceftazidime or avibactam was observed after multi-dose administration of CAZ-AVI for 11 days. Both ceftazidime and avibactam are eliminated primarily by the kidney, with the majority of the dose (80-90% ceftazidime and 85% avibactam) recovered as unchanged drug in urine. The terminal elimination half-life ($T_{½}$) of ceftazidime and of avibactam is approximately 2 h in patients with normal renal function and substantially prolonged in patients with renal impairment, necessitating reduction of dose and prolongation of the dosing interval in patients with creatinine clearance (CrCL) less than 50 mL/min. A Phase 1 study conducted with CAZ-AVI in healthy adult subjects demonstrated that ceftazidime and avibactam are able to penetrate into bronchial epithelial lining fluid (ELF) to a similar extent and with similar kinetics. The exposure of both drugs in the lung was approximately 30-35% of the exposure in plasma.

The potential for DDIs with CAZ-AVI is low based on the following: both ceftazidime and avibactam undergo limited metabolism; avibactam showed no significant inhibition or induction of cytochrome P450 (CYP) enzymes in vitro, and ceftazidime also showed no CYP induction potential; both avibactam and ceftazidime have low binding to human plasma proteins; and, avibactam and ceftazidime did not inhibit any major renal or hepatic transporters in vitro in the clinically relevant exposure range. Avibactam was shown to be a substrate of human organic anion transporter (OAT)1 and OAT3 in vitro, which may contribute to its active secretion by the kidneys. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited (by 56% to 70%) by probenecid, a potent OAT inhibitor. The clinical impact of potent OAT inhibitors on the PK of avibactam is not known.

Data from Phase 1 studies demonstrated that there was no PK interaction between ceftazidime and avibactam, and no PK interaction between ceftaroline fosamil and avibactam. In addition, a Phase 1 study showed no PK interaction between CAZ-AVI and MTZ, supporting the concomitant use of MTZ in cIAI patients.

1.3.2.4 CAZ-AVI PK/PD Target Attainment Analyses

Data from the Phase 1 CAZ-AVI and CXL studies were used along with data collected from subjects with cIAI and cUTI in the Phase 2 CAZ-AVI studies to develop population PK models for avibactam and ceftazidime. These population PK models were then used to explore PK/PD relationships in the Phase 2 studies and to conduct simulations to evaluate the probability of joint PK/PD target attainment (PTA) for ceftazidime and avibactam. The PTA analyses were used to support the proposed breakpoints, CAZ-AVI dose selection for Phase 3 studies, and to justify the proposed marketed dose with dose adjustments for renal impairment.

Based on in vitro and in vivo nonclinical studies, the PK/PD targets associated with efficacy of CAZ-AVI have been shown to be the percent of time that free drug concentrations are above the MIC over a dose interval (%*f*T > MIC) for ceftazidime and percent of time that free drug concentrations are above the threshold concentration over a dose interval (%*f*T > C_T) for avibactam. Because an exposure-response relationship could not be established with data from the Phase 2 studies due to the limited exposure range, PK/PD targets from nonclinical studies were used in simulations to assess the PTA. These targets were based on hollow fiber studies and animal models of infection with CAZ-R *Enterobacteriaceae* and *P. aeruginosa*. Four joint PK/PD targets were evaluated, with the most conservative target being 50% *f*T > CAZ-AVI MIC for ceftazidime and 50% *f*T > C_T of 1 mg/L for avibactam.

PK/PD target attainment analyses demonstrated > 90% joint target attainment with the proposed labeled dose of CAZ-AVI (2.5 g; 2.0 g ceftazidime + 0.5 g avibactam q8h) infused over 2 h at MICs up to 8 mg/L (Table 4). The population PK models used in the simulations included subject effects on the clearance of both ceftazidime and avibactam, with cIAI subjects having faster clearance (and thus lower plasma exposure) than healthy subjects or cUTI subjects. The PTA for cUTI subjects is therefore higher than the PTA presented in Table 4 for cIAI subjects.

Table 4. Percentage of Simulated cIAI Subjects Achieving PK/PD Targets at the Proposed Label Dose of CAZ-AVI Infused q8h over 2 h

CAZ-AVI MIC (mg/L)	*Percentage of Simulated Subjects Achieving PK/PD Target* [a, b]
2	98.9
4	98.9
8	98.1
16	50.8
32	1.3

a 5000 simulated cIAI subjects with normal renal function (CrCL > 80 mL/min).

b PK/PD target for ceftazidime is 50% *f*T > CAZ-AVI MIC and for avibactam is 50% *f*T > 1 mg/L.

Of note, the proposed, labeled CAZ-AVI dose of 2.5 g (2.0 g ceftazidime + 0.5 g avibactam) administered q8h as a 2-h IV infusion, based on target attainment findings, utilizes a longer infusion time than that in the Phase 2 cIAI study (CAZ-AVI was infused over 30 minutes) and a higher dose and longer infusion time than that in the Phase 2 cUTI study (CAZ-AVI 0.625 g [0.5 g ceftazidime + 0.125 g avibactam] was administered q8h as a 30-minute IV infusion). For the latter study, dose selection was based on the US labeling of ceftazidime for urinary tract infection (UTI) (FORTAZ package insert, 2010), with an assumption that high urinary concentrations of ceftazidime and avibactam would be achieved due to predominately renal excretion of both compounds. While the dosage regimen used in Study NXL104/2001 was considered sufficient to cover the majority of *Enterobacteriaceae* in the urine, it did not take into account the importance of adequate drug concentrations at extra-urinary sites or for infections due to pathogens with MICs close to the breakpoint. Patients with cUTI can have associated bacteremia, pyelonephritis, renal parenchymal abscess, and perinephric abscess. Such extra-urinary involvement may not be initially evident, and administration of a dosage adequate to produce sufficient tissue and plasma concentrations would be important (Sobel and Kaye, 2010). The higher dose and longer infusion time of the proposed CAZ-AVI dosage regimen for cUTI will ensure adequate systemic exposure and provide coverage for pathogens with higher MICs. Specifically, the proposed dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h infused over 2 h, based on simulations of plasma rather than urinary concentrations, results in adequate target attainment to support a PK/PD "susceptible" breakpoint of ≤ 8 mg/L.

1.3.3 CAZ-AVI Efficacy in Humans

The current NDA relies, in part, on prior efficacy findings for ceftazidime alone, which are detailed in Section 3.0. Clinical efficacy data from completed Phase 2 studies and the ongoing Resistant Pathogen study (Section 4.5)—in combination with the historical efficacy of ceftazidime against CAZ-S pathogens (Section 3.0)—help bridge the previously-described data derived from CAZ-AVI and avibactam PK/PD analyses, in vivo animal models, and Phase 1 studies to the management of serious MDR or CAZ-NS Gram-negative infections in hospitalized patients.

The clinical studies supporting clinical efficacy in cIAI, cUTI, and in infections with limited treatment options caused by CAZ-NS (CAZ-R or ceftazidime-intermediate [CAZ-I]) aerobic Gram-negative pathogens include: the Clinical Pharmacology ELF study (demonstrating penetration of avibactam into lung tissue and supporting a favorable PTA analysis for pneumonia as discussed in Section 4.4.1), the Phase 2 studies in cIAI and cUTI, and the interim data from the ongoing Resistant Pathogen study (in subjects infected with CAZ-NS pathogens in cIAI and cUTI).

Efficacy data from the following studies will be summarized here: (a) the Phase 2 cIAI study (NXL104/2002), (b) the Phase 2 cUTI study (NXL104/2001), and (c) the ongoing Phase 3 Resistant Pathogen study (D4280C00006). As the Phase 2 cIAI and cUTI studies enrolled subjects infected with either CAZ-S or CAZ-NS pathogens—and the ongoing Resistant Pathogen study enrolled only subjects infected with CAZ-NS pathogens—efficacy outcomes will also be described for a pooled population of subjects with cIAI and cUTI caused by CAZ-NS pathogens across all 3 studies (Section 4.5.3).

1.3.3.1 Phase 2 cIAI Study (NXL104/2002)

Study Design

Study NXL104/2002 was a descriptive, double-blind trial that enrolled subjects with cIAI. Subjects were randomized 1:1 to either CAZ-AVI 2.5 g (2.0 g ceftazidime + 0.5 g avibactam) administered q8h as a 30-minute IV infusion plus MTZ 0.5 g IV q8h (for coverage of anaerobes) (CAZ-AVI + MTZ) or to meropenem 1 g IV q8h. Concomitant use of antibiotics with coverage limited to Gram-positive pathogens was permitted in subjects for whom methicillin-resistant *Staphylococcus aureus* (MRSA) or enterococci were suspected or documented pathogens. The expected duration of treatment was 5 to 14 days. The primary efficacy endpoint was the clinical response at TOC.

Demographics and Baseline Characteristics

Overall, 102 subjects were randomized into each treatment group; 1 subject randomized to the CAZ-AVI + MTZ group did not receive study drug. Most treated subjects (92.6%) completed study drug therapy and baseline characteristics were balanced across treatment groups. The majority of subjects were male (75.3%), white (62.6%), and had Acute Physiology, Age, Chronic Health Evaluation (APACHE) II scores ≤ 10 (82.8%). Their mean (SD) age was 42.3 (16.76) years.

The types and sites of infection and operative procedures were similar between treatment groups. Nearly all subjects had pre-operative infections and the majority (90%) underwent open laparotomy as the initial surgical intervention. The most common anatomical origin of cIAI was the appendix (48.3% of subjects). These baseline characteristics are similar to those reported among subjects enrolled in recent Phase 3 cIAI studies.

The majority of subjects (82.8%) had infections caused by pathogens in the *Enterobacteriaceae* family, with *E. coli* being the most common (70% of subjects). The CAZ-AVI MIC_{90} and MIC ranges associated with *E. coli* were 0.25 mg/L and ≤ 0.03 to 2 mg/L, respectively, and the meropenem MIC_{90} and MIC ranges associated with *E. coli* were 0.015 mg/L and ≤ 0.004 to 0.03 mg/L, respectively. *P. aeruginosa* was the most commonly isolated non-fermenting Gram-negative pathogen. Approximately two-thirds of subjects had monomicrobial infections. Bacteremia at baseline was present in 7.5% of subjects. Thirty percent (53/174) of subjects in the microbiological Modified Intent-To-Treat (mMITT) Population were infected with a CAZ-NS pathogen(s).

Primary & Secondary Efficacy Analyses

The primary efficacy analysis was the clinical cure rate at TOC in the mMITT Population. The clinical cure rates were 82.4% in the CAZ-AVI + MTZ group and 88.8% in the meropenem group (Table 5). The majority of the treatment difference is due to an imbalance in the indeterminate rate.

Table 5. Primary Efficacy Endpoint: Clinical Response at TOC – Study NXL104/2002 (cIAI)

Population Response	***CAZ-AVI + MTZ n (%)***	***Meropenem n (%)***	***Difference [95% CI]***
mMITT	**N = 85**	**N = 89**	
Cure	70 (82.4)	79 (88.8)	-6.4 [-17.3, 4.2]
Failure	7 (8.2)	5 (5.6)	2.6
Indeterminate	8 (9.4)	5 (5.6)	3.8

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; MTZ = metronidazole.

The primary efficacy results are supported by consistent findings in analyses of by-subject clinical cure rates at End of Intravenous Therapy (EOIV) and LFU in the mMITT Population. The clinical cure rates at EOIV and LFU were similar between the CAZ-AVI and meropenem groups (91.8% vs. 91.0% and 83.5% vs. 86.5%, respectively).

By-pathogen clinical cure rates at TOC in the mMITT Population demonstrate similar clinical cure rates between treatment groups for Gram-negative aerobic pathogens including *Enterobacteriaceae* and *P. aeruginosa* (Section 4.5.1.4.2.2).

1.3.3.2 Phase 2 cUTI Study (NXL104/2001)

Study Design

Study NXL104/2001 was a descriptive, investigator-blinded trial that enrolled subjects with cUTI. Subjects were randomized 1:1 to CAZ-AVI 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) administered q8h as a 30-minute IV infusion or imipenem-cilastatin (hereafter imipenem) 0.5 g IV every 6 hours (q6h). As previously noted in Section 1.3.2.4, the dosage of CAZ-AVI was based on the US labeling for ceftazidime (FORTAZ package insert, 2010) and a 4:1 ratio of ceftazidime:avibactam; this dosage is 4-fold lower than the proposed labeled dose. Subjects received at least 4 days of IV study drug, after which they could be switched to open-label oral therapy (ie, ciprofloxacin 500 mg administered every 12 hours [q12h]) if they met protocol-specified criteria for clinical improvement, to complete a minimum of 7 days and a maximum of 14 days of total antibiotic therapy (IV plus oral therapy). The primary efficacy endpoint was the microbiological outcome at TOC.

Demographics and Baseline Characteristics

Overall, 137 subjects were randomized to study drug, 69 to CAZ-AVI and 68 to imipenem; 1 subject in each treatment group did not receive study drug. The treatment groups were balanced based on demographic and other baseline characteristics. Subjects in the mMITT Population were predominately female (75.8%) and white (64.2%). Mean (SD) age was 47.1 (17.9) years. Approximately two-thirds of subjects had acute pyelonephritis. These baseline characteristics are similar to those reported among subjects enrolled in recent Phase 3 cUTI studies.

The majority of subjects (94.7%) had infections caused by pathogens in the *Enterobacteriaceae* family, with *E. coli* being the most common (90% of subjects); Bacteremia at baseline was present in 6.3% of subjects. The CAZ-AVI MIC_{90} and range for *E. coli* were 0.25 mg/L and ≤ 0.03 to 0.25 mg/L, respectively, and the imipenem MIC_{90} and range for *E. coli* were 0.12 mg/L and 0.06 to 0.25 mg/L. A third of subjects in the mMITT Population (32/95) were infected with a CAZ-NS pathogen(s) at baseline.

Primary & Secondary Efficacy Analyses

The primary efficacy analysis was the favorable microbiological outcome rate at TOC in the mMITT Population (Table 6). The favorable microbiological outcome rate in the CAZ-AVI group was 67.4%, compared with 63.3% for the imipenem group.

Table 6. Primary Efficacy Endpoint: Microbiological Response Rates at TOC – mMITT Population, Study NXL104/2001 (cUTI)

Population Outcome	*CAZ-AVI n (%)*	*Imipenem n (%)*	*Difference [95% CI]*
mMITT	**N = 46**	**N = 49**	
Favorable	31 (67.4)	31 (63.3)	4.1 [-15.1, 22.9]
Unfavorable	10 (21.7)	14 (28.6)	-6.8
Indeterminate	5 (10.9)	4 (8.2)	2.7

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

The primary efficacy results are supported by results analyzing clinical cure and favorable microbiological response rates at EOIV and LFU. At the EOIV, the favorable microbiological outcome rate was 87.0% in the CAZ-AVI group and 91.8% for the imipenem group, and decreased similarly in both treatment groups over the course of the study (TOC results previously presented in Table 6); at the LFU visit, the favorable microbiological outcome rate was 50.0% in the CAZ-AVI group and 46.9% in the imipenem group. The decrease in efficacy over time in cUTI trials is typical as outcomes of microbiological persistence are carried forward, indeterminate responses are included in the denominator (thereby representing non-favorable responses), and asymptomatic microbiological recurrences over time are not uncommon in cUTI (Redman et al, 2010; Wells et al, 2004).

The clinical cure rates at EOIV and TOC were 93.5% vs. 93.9% and 80.4% vs. 73.5% for the CAZ-AVI vs. imipenem groups, respectively. Sustained clinical cure at LFU was achieved in approximately two-thirds of subjects in both treatment groups.

By-pathogen favorable microbiological outcome rates at TOC in the mMITT Population demonstrated similar microbial eradication rates between treatment groups for *Enterobacteriaceae* (Section 4.5.2.4.2.3). At TOC, eradication of *E. coli*, the predominant uropathogen isolated, was consistent with the primary outcome results (72.1% for the CAZ-AVI group vs. 61.9% for the imipenem group). Persistence (defined as urine culture taken any time after ≥ 48 h of therapy that grew ≥ 10^4 CFU/mL of an original uropathogen) occurred in all 5 subjects (3 CAZ-AVI and 2 imipenem) infected with *P. aeruginosa*. Of note, the dose of CAZ-AVI used in this study (0.5/0.125 g) is lower than the proposed labeled dose (2/0.5 g) and the imipenem dose used in this study (0.5 g q6h) was lower than that recommended for moderate to severe infections due to *Pseudomona*s (ie, 1 g q8h or q6h; PRIMAXIN package insert, 2012). In contrast, all cIAI subjects infected with *P. aeruginosa* and treated with CAZ-AVI at the proposed dose were clinically cured and had a favorable microbiological response (Section 4.5.1.4.2.2).

1.3.3.3 Efficacy in cIAI and cUTI Caused by CAZ-NS Pathogens

Subjects with CAZ-NS pathogens represent a key subgroup and analyses of the response rates for these subjects is of particular importance to demonstrate the efficacy of CAZ-AVI in the treatment of cIAI, cUTI, and for infections with limited treatment options. For the purpose of these analyses, CAZ-NS pathogens are defined as bacterial isolates whose susceptibility results are classified as "intermediate" or "resistant" using CLSI methodology (CLSI, 2013). Specifically, for *Enterobacteriaceae* and *P. aeruginosa*, CAZ-NS was defined as ceftazidime MIC ≥ 8 mg/L and MIC ≥ 16 mg/L, respectively.

These analyses include data from an interim analysis of the ongoing Resistant Pathogen study. In the mMITT Population, 85 subjects were infected with a CAZ-NS pathogen in combined Phase 2 studies (cIAI n = 53; cUTI n = 32) and 48 subjects in the ongoing Resistant Pathogen study (44 with cUTI and 4 with cIAI).

Results for subjects infected with a CAZ-NS pathogen in the Phase 2 studies were pooled with results of subjects enrolled in the Resistant Pathogen study to provide additional supportive evidence of the efficacy of CAZ-AVI for infections caused by CAZ-NS pathogens. The pooled analysis of all subjects with CAZ-NS pathogens is presented in accordance with the *Draft Guidance for Industry, Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (FDA, Jul 2013) which, in the context of a "prospective active-controlled clinical trial in patients with serious bacterial disease and unmet medical need", states that "such a trial can be conducted in a patient population enriched for an unmet need... The trial...(also) could enroll patients with bacterial disease at any one of several different body sites." The Sponsor acknowledges that the pooling of subjects with CAZ-NS pathogens within each indication and across both indications was not prospectively planned and that limitations of interpreting this data exist (discussed further in Section 4.5.3.4.1); however, within each indication, similar outcomes and associated differences between treatments were observed.

Data are pooled for each indication (cIAI in Section 4.5.3.1 and cUTI in Section 4.5.3.2) and for the total pool of subjects with CAZ-NS pathogens across both indications (Section 4.5.3.4).

Design of the Ongoing Resistant Pathogen Study (D4280C00006)

The Resistant Pathogen study (Study D4280C00006) is an ongoing, Phase 3 multinational, multicenter, randomized, open-label, study in hospitalized adult subjects with cIAI or cUTI caused by CAZ-NS Gram-negative pathogens. Subjects are stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to CAZ-AVI or best available therapy (BAT), with study drug administered for 5 to 21 days.

This study utilizes the proposed labeled dosage regimen for CAZ-AVI: 2.5 g (2 g ceftazidime + 0.5 g avibactam) q8h as a 2-h IV infusion for both indications. The Sponsor-recommended BAT options in this study are meropenem, imipenem, doripenem, tigecycline, and colistin; however, investigators are not limited to these options, and choices are based on the Investigator's standard of care, local susceptibility patterns, and the local label recommendations. (Note: for the interim analysis, all subjects in the comparator group received carbapenems [eg, imipenem, meropenem], either as monotherapy or in combination with colistin or ciprofloxacin.)

Efficacy assessments are performed at end of therapy (EOT) (within 24 h after completion of the last infusion of study drug), TOC (7 to 10 days after last dose of study drug), and follow-up (28-35 days from randomization). Clinical response is evaluated by a blinded observer. Efficacy analyses included clinical and microbiological response per subject and by pathogen responses at TOC and clinical response at EOIV and LFU in the mMITT Population.

As of the interim data cutoff date for the NDA (09 Dec 2013), complete data for 48 subjects (4 subjects with cIAI and 44 subjects with cUTI) were available.

1.3.3.3.1 Efficacy in cIAI Caused by CAZ-NS Pathogens

The clinical cure rates at TOC for subjects with CAZ-NS pathogens in the mMITT Population are presented for the Phase 2 cIAI study, the Resistant Pathogen study, and the pooled cIAI studies in Table 7. The favorable clinical cure rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cIAI studies; however, the majority of the treatment difference was due to an imbalance in the indeterminate rate. These results demonstrate that avibactam extends the activity of ceftazidime against CAZ-NS pathogens causing cIAI.

Table 7. Clinical Response at TOC in Subjects with CAZ-NS Baseline Pathogens - mMITT Population, Individual cIAI Studies

	Phase 2 cIAI Study		*Resistant Pathogen study (cIAI)*		*Pooled cIAI Studies*	
Response	***CAZ-AVI[a] (N = 30) n (%)***	***Meropenem (N = 23) n (%)***	***CAZ-AVI (N = 1) n (%)***	***Comparator (N = 3) n (%)***	***CAZ-AVI (N = 31) n (%)***	***Comparator (N = 26) n (%)***
Clinical Cure	27 (90.0)	19 (82.6)	1 (100.0)	1 (33.3)	28 (90.3)	20 (76.9)
Difference (95% CI)	7.4 (-11.8, 29.0)		66.7 (-45.2, 95.0)		13.4 (-8.6, 32.2)	
Clinical Failure	2 (6.7)	1 (4.3)	0 (0)	1 (33.3)	2 (6.5)	2 (7.7)
Indeterminate	1 (3.3)	3 (13.0)	0 (0)	1 (33.3)	1 (3.2)	4 (15.4)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

1.3.3.3.2 Efficacy in cUTI Caused by CAZ-NS Pathogens

The favorable microbiological response rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cUTI studies, although the 95% confidence interval (CI) for difference between treatment groups crossed zero (Table 8). These results demonstrate that avibactam extends the activity of ceftazidime against CAZ-NS pathogens causing cUTI.

Table 8. Microbiological Response at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Individual cUTI Studies

	Phase 2 cUTI Study		***Resistant Pathogen Study (cUTI)***		***Pooled cUTI Studies***	
Response	***CAZ-AVI (N =14) n (%)***	***Imipenem (N = 18) n (%)***	***CAZ-AVI (N = 21) n (%)***	***Comparator (N = 23) n (%)***	***CAZ-AVI (N = 35) n (%)***	***Comparator (N = 41) n (%)***
Favorable	9 (64.3)	10 (55.6)	15 (71.4)	11 (47.8)	24 (68.6)	21 (51.2)
Difference (95% CI)	8.7 (-25.4, -40.2)		23.6 (-5.8, 49.2)		17.4 (-5.1, 38.0)	
Unfavorable	3 (21.4)	6 (33.3)	5 (23.8)	12 (52.2)	8 (22.9)	18 (43.9)
Indeterminate	2 (14.3)	2 (11.1)	1 (4.8)	0 (0)	3 (8.6)	2 (4.9)

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

1.3.3.3.3 Efficacy in All Subjects with CAZ-NS Pathogens Pooled – mMITT Population

The favorable microbiological response rates at TOC for subjects with CAZ-NS pathogens in the mMITT Population for the pooled cIAI and cUTI studies are presented in Table 9. The favorable microbiological response rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cIAI and cUTI studies, with the lower bound of the 95% CI for the difference between treatment groups being -0.5%.

Table 9. Microbiological Response Rates at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Pooled Studies (cIAI and cUTI)

	Pooled Studies (cIAI and cUTI)	
Response	***CAZ-AVI (N =66) n (%)***	***Comparator (N =67) n (%)***
Favorable	52 (78.8)	41 (61.2)
Difference (95% CI)	17.6 (-0.5, 29.9)	
Unfavorable	10 (15.2)	20 (29.9)
Indeterminate	4 (6.1)	6 (9.0)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

The clinical response rates at TOC for subjects with CAZ-NS pathogens in the mMITT Population for the pooled cIAI and cUTI studies are presented in Table 10. The clinical cure rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cIAI and cUTI studies, with the lower bound of the 95% CI for the difference between treatment groups being +1.3%.

Table 10. Clinical Response Rates at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Pooled Studies (cIAI and cUTI)

	Pooled Studies (cIAI and cUTI)	
Response	***CAZ-AVI (N = 66) n (%)***	***Comparator (N = 67) n (%)***
Clinical Cure	58 (87.9)	48 (71.6)
Difference (95% CI)	16.3 (1.3, 28.7)	
Clinical Failure	5 (7.6)	8 (11.9)
Indeterminate	3 (4.5)	11 (16.4)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

Similarly, by-pathogen favorable microbiological response rates at TOC for subjects with CAZ-NS pathogens for the pooled cIAI and cUTI studies were numerically higher in the CAZ-AVI group than in the comparator group. For example, eradication rates at TOC in the CAZ-AVI vs. comparator groups were 80.5% vs. 66.7% for *E. coli* and 78.6% vs. 45% for *K. pneumoniae*, respectively (Section 4.5.3.4.3.5).

These pooled data analyses from the Phase 2 studies in cIAI and cUTI and from the Resistant Pathogen study further support that avibactam extends the activity of ceftazidime against CAZ-NS pathogens causing both cIAI and cUTI. In combination with PK/PD modeling and PTA analyses, these data also provide support for the use in infections with limited treatment options in other body sites (where CAZ-AVI penetration and PTA has been established) such as HABP/VABP and bacteremia.

1.3.4 CAZ-AVI Safety

In the completed Phase 1 and Phase 2 studies, 286 adult subjects were treated with the proposed labeled dose of CAZ-AVI (2.5 g) or avibactam (0.5 g), 146 of whom (45 in Phase 1 and 101 in Phase 2) received study drug for 5 to 14 days. With the exception of a single-dose pediatric PK study, all ongoing CAZ-AVI studies are evaluating CAZ-AVI 2.5 g IV q8h infused over 2 h for 5 or more days, depending on the indication. As of 15 Jun 2014, 1351 subjects have received the proposed labeled dose regimen in the ongoing studies. For the ongoing Phase 3 studies, deaths, blinded serious adverse events (SAEs), and discontinuations of study drug due to treatment-emergent adverse events (TEAE) are reviewed.

1.3.4.1 Nonclinical Toxicology

Comprehensive animal toxicology studies were performed with avibactam alone and CAZ-AVI. There were no new or unexpected toxicological findings in rats or dogs when both drugs were administered in combination in comparison to the effects observed with ceftazidime alone, with the exception of a slight increase in local intolerance at the injection site observed in rats with the combination as compared to ceftazidime alone.

1.3.4.2 Safety of Ceftazidime Alone

Ceftazidime is a marketed antibiotic with a well-established nonclinical and clinical safety profile. In support of this 505(b)(2) submission, safety information from the global clinical experience with ceftazidime over the last 30 years was systematically reviewed, and any potential safety concerns for ceftazidime were considered relevant to CAZ-AVI. This included aggregate assessment of US and European Union product labeling for ceftazidime, signal detection analysis using the FDA Adverse Event Reporting System (AERS) database, and available ceftazidime safety information from contemporary randomized comparative studies of cIAI and cUTI. As summarized in Section 5.3.2, this review resulted in a single additional term from the FDA AERS database signal detection analysis (non-convulsive status epilepticus) that was considered potentially relevant to ceftazidime, and hence, to CAZ-AVI. Otherwise, no significant safety findings were noted for ceftazidime.

1.3.4.3 Safety of Avibactam Alone

Animal toxicology data for avibactam alone (Section 5.1) did not indicate any safety concerns with avibactam alone or with the addition of avibactam to ceftazidime aside from slightly increased local intolerance when administered in combination through a peripheral vein as compared to ceftazidime alone.

As avibactam has no effective antimicrobial activity at concentrations achieved in humans, no safety data exist on the use of avibactam alone in infected patients. In the completed Phase 1 Clinical Pharmacology studies, healthy volunteers and subjects from special populations (ie, renal impairment, elderly) were administered avibactam alone. Table 11 presents a summary of adverse events in subjects given avibactam alone and those given CAZ-AVI in the pooled completed Clinical Pharmacology studies. The incidence of adverse events in the subjects receiving avibactam alone was generally lower than that observed with CAZ-AVI; however, direct comparison is limited based on differences in dosing regimens and study design in the studies evaluating CAZ-AVI versus those evaluating avibactam alone. The higher incidence of adverse events in the subjects from the Special Population group that received avibactam alone likely represents the higher incidence for adverse events one would expect overall in in elderly subjects or subjects with renal impairment.

Table 11. Summary of Adverse Events for Subjects Receiving Avibactam alone or CAZ-AVI, Clinical Pharmacology Studies — Safety Population

Subjects with:	*CAZ-AVI*	*Avibactam Alone*		
	Healthy Population (N = 191) n (%)	***Healthy Population (N = 163) n (%)***	***Special Population (N = 41) n (%)***	***Total (N = 204) n (%)***
Any TEAE	76 (39.8)	27 (16.6)	15 (36.6)	42 (20.6)
Any AE leading to study drug discontinuation	1 (0.5)	0	0	0
Any death or SAE	0	0	0	0

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Adverse events observed in > 1 subject in either the subjects receiving avibactam alone or those receiving CAZ-AVI in the completed Clinical Pharmacology studies are presented in Section 5.2.2. The most frequent adverse events (occurring in ≥ 2%) in subjects receiving avibactam alone were headache, diarrhea, and application site bruise; and for CAZ-AVI were headache, urine odor abnormal, and diarrhea. The majority of adverse events were mild and none were reported to be severe.

In summary, based on the completed Clinical Pharmacology studies and the toxicology data, the safety profiles for avibactam alone and CAZ-AVI appear favorable.

1.3.4.4 CAZ-AVI Safety in Phase 2 cIAI and cUTI Studies

1.3.4.4.1 Overview of Adverse Events

In the Phase 2 studies, the overall incidence of treatment-emergent adverse events (TEAEs), deaths, SAEs, and discontinuations of study drug due to TEAEs were similar between treatment groups (Table 12) in both indications.

Table 12. Summary of Adverse Events by Treatment Group, Phase 2 Studies — Safety Population

Subjects with:	***cIAI NXL104/2002***		***cUTI NXL104/2001***	
	CAZ-AVI + MTZ (N = 101) n (%)	***Meropenem (N = 102) n (%)***	***CAZ-AVI (N = 68) n (%)***	***Imipenem (N = 67) n (%)***
Any TEAE	65 (64.4)	59 (57.8)	46 (67.6)	51 (76.1)
Death	3 (3.0)	2 (2.0)	0	1 (1.5)
Any SAE	9 (8.9)	11 (10.8)	6 (8.8)	2 (3.0)
Discontinuation of study drug due to TEAE	5 (5.0)	3 (2.9)	2 (2.9)	0

Abbreviations: MTZ = metronidazole; TEAE = treatment-emergent adverse event.

1.3.4.4.2 Common Adverse Events

In the Phase 2 cIAI study in which CAZ-AVI subjects received the proposed labeled dose infused over 30 minutes, the most common TEAEs (occurring in 13.9% to 8.9% of subjects) in the CAZ-AVI + MTZ group were vomiting, nausea, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, and pyrexia. The most common TEAEs in the meropenem group (occurring in 14.7% to 6.9% of subjects) were AST increased, alanine aminotransferase (ALT) increased, pyrexia, and blood alkaline phosphatase increased (Section 5.2.2). Most TEAEs were mild or moderate in severity. No individual severe TEAE occurred in more than 2 (2.0%) subjects in either treatment group.

In the Phase 2 cUTI study in which CAZ-AVI was administered at lower than the proposed labeled dose (ie, 0.625 g IV q8h), the most common TEAEs (occurring in 19.1% to 10.3% of subjects) in the CAZ-AVI group were headache, anxiety, and constipation. The most common TEAEs (occurring in 31.3% to 10.4% of subjects) in the imipenem group were headache, diarrhea, and anxiety. Most TEAEs were mild or moderate in severity. No individual severe TEAE was reported for more than 1 (1.5%) subject in either treatment group.

1.3.4.4.3 Deaths

In the Phase 2 studies, 6 deaths were reported during the study periods (3 CAZ-AVI, 3 comparator). One additional death (CAZ-AVI group) was reported spontaneously after the study. The causes of death among subjects treated with CAZ-AVI were 1 each of septic shock, multiple organ failure, sepsis, and cardiac arrest. None of the deaths was assessed by the investigator or Sponsor to be caused by study drug. The causes of death are consistent with those expected in the population enrolled in these studies.

1.3.4.4.4 Serious Adverse Events

The incidence of SAEs was similar between treatment groups in both Phase 2 studies (Table 12). No SAE occurred in more than 1 subject in any treatment group within either Phase 2 study, with the exception of intestinal obstruction (n = 2; 2%) in the meropenem group of the cIAI study. For 5 subjects, the Investigator considered the SAE(s) related to study drug, including 1 CAZ-AVI-treated subject in the cIAI study (SAEs of hepatic enzyme increased and localized intra-abdominal fluid collection), 3 CAZ-AVI-treated subjects in the cUTI study (SAEs of diarrhea, accidental overdose, acute renal failure), and 1 imipenem-treated subject in the cUTI study (SAE of blood creatinine increased). Two of these 5 SAEs (hepatic enzyme increased and accidental overdose) led to premature discontinuation of study drug. More detail on these SAEs is provided in Section 5.2.2.3.

1.3.4.4.5 Adverse Events Leading to Premature Discontinuation of Study Drug

Discontinuation rates in the Phase 2 studies were low and similar between treatment groups. Three CAZ-AVI subjects discontinued study drug due to rash; otherwise, no single TEAE leading to premature discontinuation of study drug occurred in more than 1 subject in a Phase 2 study.

1.3.4.4.6 Laboratory and Electrocardiogram Findings

Results of liver function tests, renal function tests, and hematology tests are summarized in Section 5.2.3. Safety concerns were not observed based on a systematic review of other routine chemistry, hematology, and coagulation data.

A thorough QT study was performed in which 3 g of ceftazidime and 2 g of avibactam were administered. Results demonstrated that a supratherapeutic dose of CAZ-AVI did not significantly prolong the QT interval corrected for heart rate (QTc). In the Phase 2 studies, one CAZ-AVI-treated subject (cUTI study) and 1 meropenem-treated subject (cIAI study) each had 1 QT interval corrected by the Fridericia formula (QTcF) > 500 msec (and change from baseline > 60 msec) during the study. Both had a medical history of preexisting cardiac disease and neither experienced a cardiac TEAE associated with the QTcF prolongation.

1.3.4.4.7 Analysis of Topics of Special Interest

Pre-specified Medical Dictionary for Regulatory Activities (MedDRA) preferred terms were reviewed to identify adverse events and potentially clinically significant (PCS) laboratory values representing potential safety concerns for 5 topics of special interest: liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders. These 5 topics of special interest were selected based on relevance to the known safety profile of ceftazidime (eg, hypersensitivity) and/or other cephalosporins (eg, hematologic disorders representing low blood counts) or being a known severe complication for any drug (eg, liver disorders). On review of the above topics no additional safety concern was noted. Specifically, there was no anaphylactic reaction, hemolytic anemia, or *Clostridium difficile*-associated diarrhea (CDAD) observed in the Phase 2 program (Section 5.2.3).

1.3.4.5 CAZ-AVI Safety in Ongoing Studies

For each of the indications under study, the incidences of deaths, SAEs, and discontinuations due to a TEAE in the ongoing Phase 3 studies are comparable to those from the completed Phase 2 studies and/or relevant literature (Section 5.2.2).

1.4 BENEFIT/RISK SUMMARY

The prevalence and spread of MDR Gram-negative pathogens are increasing, resulting in the common occurrence of difficult-to-treat, serious infections within a variety of indications (eg, cIAI, cUTI, and HABP/VABP). Despite advances in medical care and antimicrobial therapy, these Gram-negative pathogens are increasingly important causes of mortality and prolonged hospitalization in the US. New antimicrobials with enhanced spectrum of activity are needed for such infections, especially given the rising incidence of highly-resistant and highly-virulent pathogens, such as carbapenem-resistant *Enterobacteriaceae*, ESBL-producing Gram-negative bacilli, and MDR *P. aeruginosa.*

The extensive data package described here, including the established efficacy of ceftazidime, in vitro evidence that avibactam extends the activity of ceftazidime vs. CAZ-NS isolates, PK/PD target attainment analyses, and data from in vivo animal models of infection, is predictive of the clinical efficacy of CAZ-AVI. Clinical efficacy data from the Phase 2 cIAI, Phase 2 cUTI, and an ongoing Resistant Pathogen study provide supportive evidence that CAZ-AVI administered at a dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h is effective for the treatment of cIAI and cUTI caused by common Gram-negative pathogens—including CAZ-NS pathogens—and is a beneficial adjunct to the current armamentarium of parenteral antimicrobial therapy for serious and severe infections. Among subjects with cIAI or cUTI caused by CAZ-NS pathogens, favorable microbiological and clinical response rates were numerically higher in the CAZ-AVI group than in the comparator group (all of whom received carbapenem-based regimens). In addition to cIAI and cUTI, available evidence supports a favorable benefit-risk balance for the use of CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h in adults with infections caused by CAZ-NS Gram-negative pathogens in the face of limited or no other available therapeutic options.

Although Phase 3 cIAI and cUTI studies based on a traditional development program are in progress, waiting for these results would delay the review for approval of CAZ-AVI until mid to late 2016. An urgent unmet need exists now and is likely to increase over time until new antimicrobial therapies are developed that address the rising prevalence of MDR Gram-negative pathogens (Section 1.1). For example, the emergence and spread of CRE represent an ominous threat, as these pathogens are often MDR or pan-resistant to all effective antibiotics—leaving no treatment options or options limited to toxic agents such as colistin. Although currently uncommon, the rates of CRE have continued to rise since their emergence. For instance, the number of UTIs caused by CRE increased from 0% in 2000 to 2.3% in 2009 (Zilberberg and Shorr, 2013a). In addition, CRE currently account for approximately 4% of bloodstream infections and 5% of pneumonia cases (Zilberberg and Shorr, 2013b). The incidence of CRE varies by region, and outbreaks of infections caused by CRE have occurred over recent years. New CRE-active antimicrobials are clearly needed now, as recognized by the CDC who classifies CRE as an Urgent Threat Level.

The cumulative CAZ-AVI safety database includes 1896 subjects who have received CAZ-AVI or avibactam alone in completed or ongoing studies. Safety data from nonclinical studies and completed Clinical Pharmacology studies demonstrate that avibactam does not significantly alter the established safety profile of ceftazidime. In addition, safety data from completed Phase 2 cIAI and cUTI studies, interim safety data from ongoing Phase 3 studies in cIAI, cUTI, and HABP/VABP, along with the extensive clinical experience with ceftazidime, support the determination that CAZ-AVI can be safely administered at the proposed dose regimen for the treatment of patients with cIAI and cUTI.

The totality of the safety and efficacy data supports a positive benefit:risk balance for the use of CAZ-AVI in the current and future evolving environment of microbial resistance in serious infections caused by MDR Gram-negative pathogens. CAZ-AVI addresses distinct areas of unmet medical need and has the potential to provide a significant benefit in the treatment of cIAI and cUTI and for infections such as HABP/VABP and bacteremia where limited or no alternative therapies are available. The potential clinical benefit is evidenced by its in vitro, in vivo (in animal models of infection), and clinical efficacy against CAZ-NS Gram-negative infections while maintaining a safety profile consistent with that of ceftazidime and the cephalosporin class.

2.0 CAZ-AVI DEVELOPMENT PROGRAM

2.1 REGULATORY HISTORY

The original Investigational New Drug (IND) application for CAZ-AVI was submitted on 07 Jan 2008 by Novexel SA for the treatment of Gram-negative bacterial infections (IND 101,307). All rights and responsibilities for the IND were transferred from Novexel to AstraZeneca Pharmaceuticals on 16 Apr 2010, and then from AstraZeneca to Cerexa, Inc. (a subsidiary of Actavis plc) on 05 Oct 2011. Cerexa and AstraZeneca are collaborative partners for the global development of CAZ-AVI, with Cerexa having the US regulatory responsibilities and commercial rights.

As described in Section 1.2, the overall data package to support the approval of CAZ-AVI through the 505(b)(2) registration pathway comprises data on ceftazidime alone, avibactam alone, and CAZ-AVI. This includes data from nonclinical toxicology studies; microbiological surveillance data in a large number of clinically relevant pathogens; in vitro PK/PD studies; data from in vivo animal models of infection including pyelonephritis; pneumonia, septicemia, and meningitis; Phase 1 clinical pharmacology studies in healthy subjects and special populations; robust PK/ PD target attainment analyses; and the clinical experience with ceftazidime alone based on a meta-analysis of data from the published clinical literature and review of post-marketing safety information. In addition, descriptive efficacy and safety data from two Phase 2 studies in hospitalized adults with cIAI and cUTI, along with interim efficacy data from an ongoing Phase 3 study of cIAI and cUTI caused by CAZ-NS (including CAZ-R and CAZ-I) Gram-negative pathogens, provide evidence of the clinical efficacy of CAZ-AVI against common Gram-negative pathogens causing serious bacterial infections, including MDR strains.

To date, the CAZ-AVI Clinical Development Program includes 13 completed clinical studies of CAZ-AVI or avibactam alone. This includes 11 completed Phase 1 Clinical Pharmacology studies (10 from the CAZ-AVI development program, and 1 from the CXL program) along with 2 completed Phase 2 efficacy and safety studies in cIAI and cUTI (Table 13).

The completed Clinical Pharmacology studies evaluated the PK of avibactam alone and in combination with ceftazidime in (1) healthy adult subjects (including one study in healthy Japanese subjects); (2) ELF in healthy adult subjects; (3) subjects with renal impairment including subjects with end-stage renal disease (ESRD) who were receiving intermittent hemodialysis; and (4) male and female subjects 65 years of age and older. The DDI potential was investigated between ceftazidime and avibactam and between CAZ-AVI and MTZ. A Clinical Pharmacology study was also conducted to provide information on the effect of CAZ-AVI on the QTc interval.

Table 13. CAZ-AVI Efficacy and Safety Clinical Development Program –Completed Clinical Studies

Study ID	*Study Type/Population*
Clinical Pharmacology Studies with CAZ-AVI or Avibactam Alone	
NXL104/1001	Single-dose escalation PK/Healthy adults
NXL104/1002	Multiple-dose escalation PK/Healthy adults
NXL104/1003	Single-dose PK avibactam/renally impaired and healthy adults
NXL104/1004	Single-dose PK avibactam, age and gender/Healthy adults
D4280C00007	Thorough QT study/Healthy adults
D4280C00008	DME/Healthy adults
D4280C00009	Epithelial lining fluid/Healthy adults
D4280C00010	Single- and multiple-dose PK, Japanese subjects/Healthy adults
D4280C00011	DDI PK, ceftazidime and avibactam/Healthy adults
D4280C00012	DDI PK, metronidazole/Healthy adults
Clinical Pharmacology Study with Avibactam Alone (From CXL Development Program)	
CXL-PK-01	DDI PK, ceftaroline and avibactam/Healthy adults
Phase 2 Clinical Efficacy and Safety Studies	
NXL104/2001	cUTI/Infected hospitalized adults
NXL104/2002	cIAI/Infected hospitalized adults

Abbreviations: CXL = ceftaroline fosamil-avibactam; DDI = drug-drug interaction; DME = distribution, metabolism, and excretion.

Additional studies in the CXL development program evaluated the PK of avibactam in subjects with severe renal impairment at steady-state (CXL-PK-03), in subjects with augmented renal clearance and sepsis (CXL-PK-04), and in subjects with Class I, II, and III obesity (CXL-PK-06).

2.2 ONGOING CLINICAL DEVELOPMENT PROGRAM

All ongoing studies in the Phase 3 program are evaluating the dose regimen proposed for labeling: CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h administered over 2 h, for 5 or more days, based on the indication.

Interim efficacy data from the Phase 3 Study D4280C00006, "Resistant Pathogen: cIAI and cUTI/Infected hospitalized adults" (referred to as the ongoing Resistant Pathogen study), are included in this NDA to support the use of CAZ-AVI for infections caused by CAZ-NS pathogens (Section 4.5.3.3).

High-level safety data from two ongoing, blinded Phase 3 studies—one in cIAI and one in cUTI—are included in this NDA (Section 5.2); however, unblinded safety data from three ongoing Phase 1 Clinical Pharmacology studies and unblinded safety and efficacy data from the ongoing Phase 3 studies (cIAI, cUTI, and HABP/VABP) are *not* included in the submission (Table 14). Final data for these ongoing Phase 3 studies will be reported in a supplemental NDA at a later date.

Table 14. CAZ-AVI Efficacy and Safety Clinical Development Program –Ongoing Clinical Studies

Study ID	***Study Type/Population***	***Blinded Study Design***
Phase 3 Clinical Efficacy and Safety Studies		
D4281C00001	HABP/VABP/Infected hospitalized adults	yes
D4280C00001/5[a]	cIAI/Infected hospitalized adults	yes
D4280C00002/4[b]	cUTI/Infected hospitalized adults	yes
D4280C00006	Resistant Pathogen: cIAI and cUTI/Infected hospitalized adults	no
D4280C00018	cIAI (Asia)/Infected hospitalized adults	yes
Clinical Pharmacology Studies with CAZ-AVI		
D4280C00014	Single-dose PK/Infected pediatric subjects	no
D4280C00020	Single- and multiple-dose PK (China)/Healthy adults	yes
D4280C00023	Multiple-dose, effect on intestinal flora (CAZ-AVI and CXL)/Healthy adults	no

Abbreviations: CXL = ceftaroline fosamil-avibactam.

a D4280C00001 and D4280C00005 are combined into one study database (D4280C00001/5).

b D4280C00002 and D4280C00004 are combined into one study database (D4280C00002/4).

None of the Phase 3 studies have been fully completed (ie, completed data analysis with final Clinical Study Report); however, top-line results have been released for the combined Phase 3 cIAI Studies D4280C00001/5 (RECLAIM-1/-2) (Actavis, 2014). In this pooled Phase 3 cIAI dataset, CAZ-AVI met the objective of statistical non-inferiority compared to meropenem. The primary endpoint was a clinical cure rate 28 to 35 days after randomization (TOC) in the mMITT Population, and the non-inferiority margin was 10%. The resultant lower and upper bounds of the 95% CI were -8.64% and 1.58% respectively. In addition, CAZ-AVI was effective in treating CAZ-NS pathogens. The most commonly reported TEAEs for CAZ-AVI + MTZ were diarrhea, nausea, vomiting, and fever.

Full completion of the Phase 3 cIAI and cUTI studies are targeted for late 2015, with supplemental NDAs filed a few months thereafter.

3.0 HISTORY OF CEFTAZIDIME EFFICACY

To fulfill the regulatory requirements of this 505(b)(2) NDA, the Sponsor performed a meta-analysis of the efficacy of ceftazidime alone in adult subjects with cIAI and cUTI.

A literature search was conducted on PubMed, Ovid, The Cochrane Library, and ClinicalTrials.gov, in order to identify randomized, prospective, comparative, controlled studies for a meta-analysis that had an objective of estimating the microbiological and clinical response to ceftazidime. Search interfaces included the following databases: MEDLINE, PubMed Central, National Center for Biotechnology Information (NCBI) Bookshelf, Journals@Ovid, Cochrane Database of Systematic Reviews (CDSR), and Cochrane Central Register of Controlled Trials (CENTRAL) (controlled clinical trials from MEDLINE and EMBASE); searches were limited to human and English language studies if applicable for the interface. For the purposes of this meta-analysis, cIAI was defined as intra-abdominal infection that extends beyond the hollow viscus of the intestinal tract and requires surgical intervention, and cUTI was defined as acute pyelonephritis or UTI associated with anatomical abnormalities, obstruction, or instrumentation.

The initial search identified 400 articles (112 from PubMed, 87 from Ovid, 153 from Cochrane, and 48 from ClinicalTrials.gov). From this initial pool of articles, 160 unique search results were assessed. Thirty-five studies (2 cIAI studies and 33 cUTI studies) were submitted for Sponsor review. Finally, 2 cIAI articles and 16 cUTI studies were accepted; these 18 prospective, randomized, controlled trials, published between 1983 and 1996, were included in this meta-analysis. Of note, these studies predated current regulatory guidance establishing the mMITT Population as a primary population for analysis; therefore, the meta-analysis was conducted with data from the microbiologically evaluable (ME) (or ME-like) Population.

Point estimates and corresponding 90% CIs were obtained using the weighted non-iterative method under the assumption of unequal variances of DerSimonian-Laird (DerSimonian and Laird, 1986). Data extracted included subject inclusion criteria, subject population analyzed in the efficacy analysis, study definition of presumed cIAI, definition of clinical response, study treatments (dosage/duration), and favorable clinical and microbiologic response rates. A minimum of 2 reviewers independently reviewed the data extraction to ensure accuracy.

Among subjects with cIAI in the ME-like Population, clinical cure rate at TOC was achieved in a higher proportion of those in the ceftazidime group, although the 90% CI overlapped with that of the comparator (Table 15). These data demonstrate that ceftazidime continues to be an efficacious antibiotic for the treatment of cIAI caused by CAZ-S pathogens, as the FORTAZ label indicates.

Table 15. Historical Ceftazidime Treatment of cIAI: Favorable Response at TOC – ME-Like Population

Indication **Response**	***Ceftazidime*** ***n/N (%)*** ***[90% CI]***	***Comparator(s)*** ***n/N (%)*** ***[90% CI]***
cIAI		
Clinical cure at TOC	57/67 (86.1) [76.0, 96.1]	46/67 (68.9) [36.3, 100.0]

Note: For the meta-analysis, point estimates and corresponding 90% confidence intervals were obtained using the weighted non-iterative method described by DerSimonian-Laird under the assumption of unequal variances.

Among subjects with cUTI in the ME-like Population, similar proportions of subjects in the ceftazidime and comparator groups achieved favorable microbiological response and clinical cure at TOC (Table 16). However, a major limitation with these studies is the variation in ceftazidime dosage, ranging from 1 to 6 g per day in divided doses. Other limitations included duration of therapy from 3 to 21 days, timing of the TOC assessment varied from 3 days to 6 weeks post-treatment, and varied comparators used (eg, aminoglycosides, quinolones, cephalosporins, carbapenems). In the context of these limitations, the available data demonstrate that ceftazidime continues to be an efficacious antibiotic for the treatment of cUTI caused by CAZ-S pathogens, as the FORTAZ label indicates.

Table 16. Historical Ceftazidime Treatment of cUTI: Favorable Response at TOC – ME-Like Population

Indication **Response**	***Ceftazidime*** ***n/N (%)*** ***[90% CI]***	***Comparator(s)*** ***n/N (%)*** ***[90% CI]***
cUTI		
Favorable Microbiological Response at TOC	596/682 (89.5) [85.9, 93.1]	898/1040 (85.3) [81.6, 89.0]
Clinical Cure at TOC	355/396 (92.4) [88.8, 95.9]	485/549 (89.0) [85.1, 92.9]

Abbreviations: ME = Microbiologically Evaluable; TOC = Test-of-Cure.

Note: For the meta-analysis, point estimates and corresponding 90% confidence intervals were obtained using the weighted non-iterative method described by DerSimonian-Laird under the assumption of unequal variances. For studies in which the response rate was equal to 100%, the total number of observations was adjusted by adding 0.1 so that an estimate of variance could be obtained.

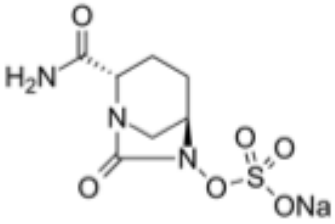
In summary, ceftazidime is a well-established 3rd-generation cephalosporin that has been used for nearly 30 years in the treatment of a variety of infections, including cIAI and cUTI. The meta-analysis described above reveals that ceftazidime remains efficacious in the treatment of such infections when caused by ceftazidime-susceptible Gram-negative pathogens. However, ceftazidime is no longer reliably stable to the common TEM and SHV β-lactamases that were in existence at the time of approval. As described in Section 1.1, the emergence of ESBLs and the increasing incidence of MDR Gram-negative pathogens such as *P. aeruginosa* threaten the current and future utility of ceftazidime alone.

4.0 IN VITRO & IN VIVO EFFICACY OF CAZ-AVI

4.1 Avibactam and CAZ-AVI Characteristics

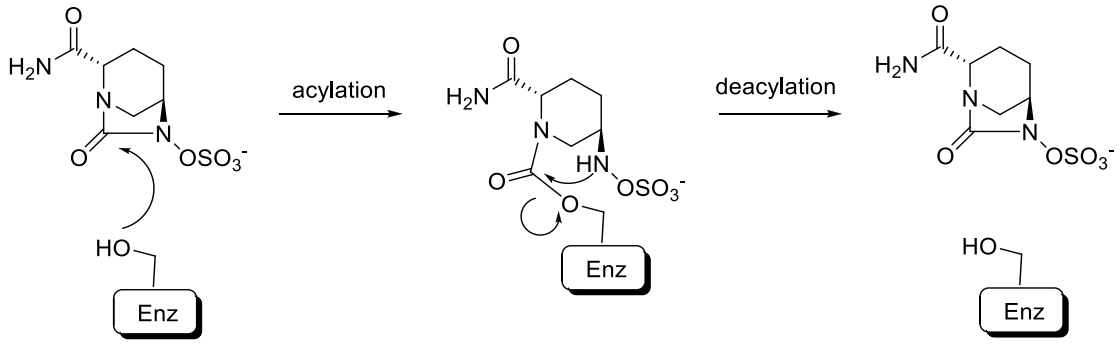
The chemical name of avibactam is sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate (structure shown in Figure 1).

Figure 1. Chemical Structure of Avibactam Sodium



In contrast to currently available BLIs, avibactam is a first-in-class non-β-lactam BLI with a unique mode of action that is driven by covalent binding and inhibition of the β-lactamase enzyme. This bond is slowly reversible; upon deacylation (and hence reversal of the covalent bond which results in the inhibition of β-lactamases) intact avibactam is released enabling the molecule to inhibit another β-lactamase (Figure 2).

Figure 2. Covalent, Reversible Mechanism of Avibactam Inhibition of Serine β lactamases



Avibactam alone has no antibacterial activity at clinically relevant doses. When combined with ceftazidime, avibactam protects ceftazidime from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of ceftazidime to include many Gram-negative bacteria normally not susceptible to ceftazidime.

Avibactam has been evaluated in biochemical assays to determine inhibitory activity against purified β-lactamase enzymes relative to other currently approved β-lactamase inhibitors. Against most Class A β-lactamases, including KPC, avibactam was a more potent inhibitor than clavulanic acid, tazobactam, or sulbactam as evidenced by lower IC_{50} values. Avibactam was also a more potent inhibitor of the Class C β-lactamases including P99 and AmpC from *P. aeruginosa.* Similar to other BLIs, avibactam does not have inhibitory activity against the Class B metallo-β-lactamases such as IMP, VIM and NDM (Ehmann et al, 2013; Livermore et al, 2008; Livermore et al, 2011; Stachyra et al, 2009) (Table 17).

The resulting combination product, CAZ-AVI, is available as a 2.5 g single-dose vial containing sterile ceftazidime pentahydrate/sodium carbonate equivalent to 2 g of ceftazidime and sterile avibactam sodium equivalent to 0.5 g avibactam. The total sodium content of the mixture is approximately 146 mg (6.4 mEq)/vial.

Table 17. Broader Spectrum of Avibactam Activity Compared to Available β-lactamase Inhibitors

β-Lactamase		Avibactam	Clavulanic Acid	Tazobactam
Class A (Serine)	TEM, SHV and ESBLs	**Yes**	Yes	Yes
	CTX-M and ESBLs	**Yes**	Yes	Yes
	PER, VEB, GES	**Yes**	Yes	Yes
	KPC	**Yes**	No	No
Class B (Metallo)	IMP, VIM, NDM	**No**	No	No
Class C (Serine)	Chromosomal *Enterobacteriaceae* AmpC	**Yes**	No	No
	Chromosomal *Pseudomonas* AmpC	**Yes**	No	No
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	**Yes**	No	No
Class D (Serine)	Penicillinase-type OXA-1, -31, -10, -13	**Variable**	Variable	Variable
	Carbapenemase-type OXA-23, -40, -48, -58	**Variable**	Variable	Variable

4.1.1 CAZ-AVI In Vitro Activity

When avibactam is tested in combination with ceftazidime it extends the antibacterial activity of ceftazidime against most β-lactamase-producing *Enterobacteriaceae* and *P. aeruginosa* that would otherwise be resistant to ceftazidime alone (Table 18). Although avibactam extends the antibacterial activity of ceftazidime against β-lactamase-producing organisms it does not compromise the activity of ceftazidime against CAZ-S Gram-negative pathogens (Table 18).

Several details should be noted when evaluating the MIC data for CAZ-AVI. Consistent with MIC testing of most other BL-BLI combinations (CLSI, 2013), CAZ-AVI MIC values are determined with ceftazidime in the presence of a fixed concentration of 4 mg/L avibactam. This provides reproducible results and allows separation of wild-type from resistant organisms (Huband et al, 2015). The fixed concentration of 4 mg/L also allows one to observe a difference in the MIC values between ceftazidime alone and CAZ-AVI against β-lactamase producing Gram-negative bacteria for which ceftazidime has reduced activity.

The fixed avibactam concentration of 4 mg/L should not be confused with the PK/PD target for avibactam in combination with ceftazidime. In vitro and in vivo PD studies have clearly demonstrated that the PK/PD target for avibactam in combination with ceftazidime is $\%fT>C_T$ of 0.25 - 1 mg/L for *Enterobacteriaceae* and *P. aeruginosa* (Section 4.2.2). Furthermore, studies in animal models of infection have shown that the proposed dosing regimen of CAZ-AVI (2.5 g IV q8h) results in predictable activity against *Enterobacteriaceae* and *P. aeruginosa* isolates with a CAZ-AVI MIC of 8 mg/L (Section 4.2.3).

Table 18. Activity of Ceftazidime and Ceftazidime-avibactam Against Ceftazidime-susceptible and Non-susceptible Gram-negative Pathogens from 2012 US Surveillance

Organism	***Phenotype (N)***	***MIC_{90} (mg/L)***	
		Ceftazidime-avibactam	***Ceftazidime***
E. coli	Non-ESBL (2439)	0.12	0.25
	ESBL[a] (328)	0.25	>32
K. pneumoniae	Non-ESBL (1551)	0.25	0.5
	ESBL[a] (296)	1	>32
	Meropenem-NS[b] (115)	2	>32
K. oxytoca	Non-ESBL (398)	0.12	0.25
	ESBL[a] (44)	1	>32
E. aerogenes	CAZ-S (275)	0.25	0.5
	CAZ-NS[b] (82)	0.5	>32
E. cloacae	CAZ-S (751)	0.25	0.5
	CAZ-NS[b] (200)	1	>32
P. aeruginosa	CAZ-S (1637)	4	4
	CAZ-NS[b] (330)	16	>32
	Meropenem-NS[b] (354)	16	>32

[a]Defined as MIC > 1 mg/L for aztreonam, ceftazidime and/or ceftriaxone
[b]Criteria as published by CLSI M100-S22, 2012

During the 2012 US surveillance program all ESBL-phenotype isolates of *Enterobacteriaceae* were characterized for the presence of specific β-lactamase genes. The MIC_{90} values for CAZ-AVI and the characterized β-lactamase-producing organisms ranged from 0.25 to 2 mg/L compared with 16 to >32 mg/L for ceftazidime alone (Table 19).

Table 19. Activity of CAZ-AVI and Comparators against Characterized β-Lactamase-producing Organisms from 2012 US Surveillance

β-Lactamase-producing organism (N)	***MIC_{90} (% Susceptible by CLSI Interpretive Criteria)***			
	CAZ-AVI	***Ceftazidime***	***Meropenem***	***Piperacillin/tazobactam***
KPC (118)	2	>32 (0.0)	>8 (0.0)	>64 (0.0)
CTM-M-15-like (288)	0.5	>32 (14.6)	≤0.06 (99.7)	>64 (67.2)
CTX-M-14-like (70)	0.25	16 (74.3)	≤0.06 (100.0)	8 (92.9)
ESBL-SHV (83)	0.25	>32 (12.0)	0.12 (98.8)	>64 (45.8)
CMY-2-like (54)	0.5	>32 (13.0)	0.12 (100.0)	>64 (81.5)

The spectrum of activity of CAZ-AVI is shown in Table 20 and includes the spectrum of ceftazidime alone but with expanded activity against β-lactamase-producing ceftazidime non-susceptible isolates of *Enterobacteriaceae* and *P. aeruginosa.* As expected, the in vitro activity of CAZ-AVI is similar to ceftazidime against CAZ-S isolates of both Gram-negative and Gram-positive pathogens. Avibactam does not extend the activity of ceftazidime against *Acinetobacter baumannii*; this is likely due to the production of common OXA β-lactamases that are not inhibited by avibactam.

Table 20. Spectrum of Activity for CAZ-AVI

Aerobic Gram-negative bacteria (including β-lactamase-producing strains) • *Citrobacter freundii* • *Citrobacter koseri* • *Escherichia coli* • *Enterobacter aerogenes* • *Enterobacter cloacae* • *Haemophilus influenzae* • *Haemophilus parainfluenzae* • *Klebsiella pneumoniae* • *Klebsiella oxytoca* • *Morganella morganii* • *Proteus* spp. (including *Proteus mirabilis* and indole-positive *Proteus*) • *Providencia stuartii* • *Pseudomonas aeruginosa* • *Pseudomonas stutzeri* • *Serratia marcescens*
Aerobic Gram-positive bacteria • *Staphylococcus aureus* (methicillin-susceptible strains only)

4.1.2 CAZ-AVI Resistance Potential

The potential for resistance development to CAZ-AVI among β-lactamase-producing *Enterobacteriaceae* and *P. aeruginosa* was assessed in laboratory studies. For most ESBL- and AmpC-producing organisms, no spontaneous mutants were identified at 4 x MIC with spontaneous mutation frequencies $\leq 10^{-9}$ (Table 21). Among the KPC-producing organisms spontaneous mutation frequencies were low and ranged from 1.8×10^{-8} to $< 10^{-9}$ at 4 x MIC and the mutation frequencies were further reduced at higher multiples of the MIC.

Table 21. Frequencies of Mutants Selected from 28 Isolates in a Single Step on Agar Containing Different MIC Multiples of CAZ-AVI, 4 mg/L

Organism	*β-Lactamase*	*MIC (mg/L)*		*Spontaneous Frequencies at*	
		CAZ	*CAZ + AVI*	*4 x MIC*	*8 x MIC*
K. pneumoniae	SHV-2	> 256	1	<	<
K. pneumoniae	SHV-2	64	0.5	<	<
K. pneumoniae	SHV-5	256	0.5	1.6×10^{-8}	<
K. pneumoniae	SHV-5	> 256	1	<	<
K. pneumoniae	CTX-M-1	64	0.5	<	<
K. pneumoniae	CTX-M-1	256	0.5	<	<
E. coli	CTX-M-15	16	0.25	<	<
E. coli	CTX-M-15	32	0.25	<	<
E. coli	TEM-10	> 256	0.5	<	<
E. coli	TEM-10	> 256	1	6.6×10^{-9}	<
K. pneumoniae	KPC	256	2	1.9×10^{-8}	3.08×10^{-9}
K. pneumoniae	KPC	128	2	1.8×10^{-8}	8.0×10^{-9}
E. cloacae	KPC	32	0.5	2.2×10^{-8}	3.71×10^{-9}
E. cloacae	KPC	32	0.5	<	1.99×10^{-9}
E. cloacae	AmpC	64	0.5	<	<
E. cloacae	AmpC	64	0.5	4.81×10^{-9}	1.92×10^{-9}
C. freundii	AmpC	256	1	<	<
C. freundii	AmpC	128	0.5	2.2×10^{-9}	2.2×10^{-9}
P. aeruginosa	AmpC	64	4	8.7×10^{-10}	<
P. aeruginosa	AmpC	64	4	<	<

Abbreviations: CAZ = ceftazidime; AVI = avibactam
< : below detection limit of 0.5×10^{-9}

The spontaneous mutants exhibited decreased susceptibility to CAZ-AVI when compared with the parent strain. Although the frequencies for selecting spontaneous mutants were low, the identified resistant mutants were further characterized to determine the molecular basis for resistance. The bla_{KPC} genes from resistant mutants of *K. pneumoniae* and *E. cloacae* revealed some sequence alterations in the Ω loop or in the immediate C-terminal side of it. The mutation in several single-step-selection mutants as well as one multi-step-selection mutant was a single Asp179Tyr substitution.

Of note, no resistant mutants of β-lactamase-producing organisms were identified in any of the animal efficacy models when CAZ-AVI was evaluated as a 4:1 ratio or with simulated human exposures of 2.5 g (2 g ceftazidime plus 0.5 g avibactam) q8h with a 2-h infusion. Furthermore, in clinical trials none of the clinical isolates from CAZ-AVI-treated subjects that persisted at the TOC or LFU visits showed resistance development during therapy as evidenced by > 4-fold increase in CAZ-AVI MIC for the baseline pathogen.

4.2 CAZ-AVI Efficacy in Nonclinical In Vitro and In Vivo Infection Models

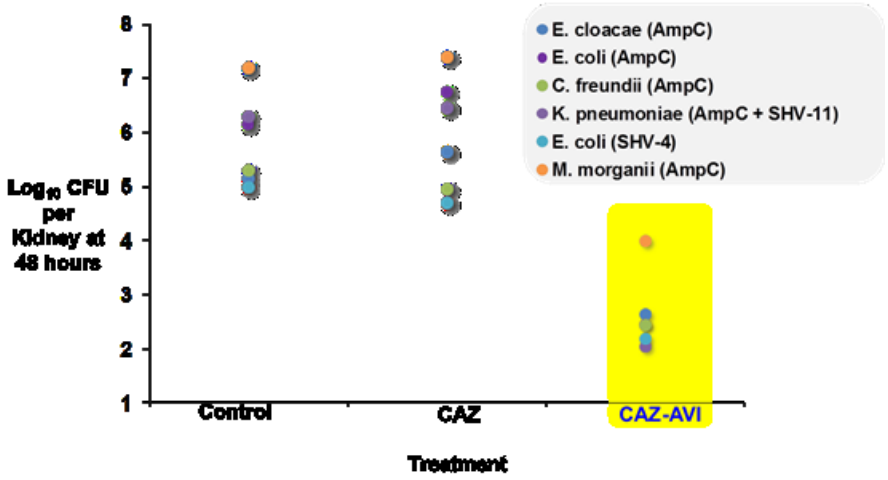
4.2.1 Proof-of-Concept Animal Models of Infection

The ability of avibactam to extend the in vivo efficacy of ceftazidime against β-lactamase-producing Gram-negative organisms has been successfully demonstrated in a wide variety of different animal infection models that included: murine peritoneal sepsis, murine neutropenic thigh infections, murine pneumonia, murine pyelonephritis, and rabbit meningitis.

4.2.1.1 Mouse Kidney Infection (Pyelonephritis) Model

Immunosuppressed mice were infected by direct inoculation of approximately 10^4 CFU of β-lactamase-producing *Enterobacteriaceae* into the kidney. CAZ-AVI and ceftazidime were administered subcutaneously at 4, 8, 24 and 32 h post infection and bacterial load assessed after 48 h. Ceftazidime was similar to the untreated control whereas CAZ-AVI treated animals showed a 2.6 to 4.5 $\log_{10}$ reduction in bacterial load (Figure 3).

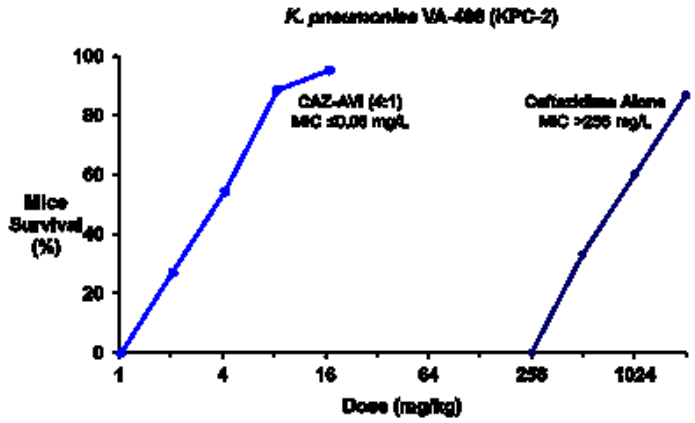
Figure 3. Efficacy of CAV-AVI and Ceftazidime Against β-lactamase-producing Enterobacteriaceae in a Murine Kidney Infection Model—Bacterial Burden at 48 h



4.2.1.2 Murine Systemic Infection (Septicemia) Models

CAZ-AVI and ceftazidime were evaluated for efficacy against a KPC-2 producing *K. pneumoniae* (strain VA-406) in a murine septicemia model. Septicemia was induced by intraperitoneal injection of organism (3.3 to 3.5 x 10^5 CFU). CAZ-AVI (4:1 ratio) and ceftazidime were administered after 30 minutes. Figure 4 shows the increased survival of mice treated with CAZ-AVI with > 90% survival at 16 mg/kg compared with > 256 mg/kg of ceftazidime alone. The addition of avibactam dramatically reduced the amount of ceftazidime to favorably treat systemic infections induced in mice.

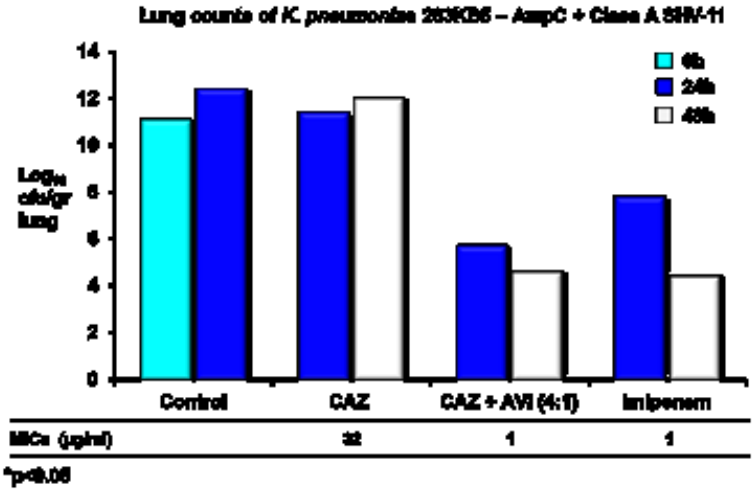
Figure 4. **Efficacy of CAZ-AVI and Ceftazidime against *K. pneumoniae* KPC-2 induced Septicemia in Mice**



4.2.1.3 Murine Pneumonia Model

Immunocompromised mice were infected intratracheally with 10^8 to 10^9 CFU *K. pneumoniae* that produced AmpC and SHV-11 β-lactamase. CAZ-AVI (4:1 ratio), ceftazidime or imipenem were administered as 150 mg/kg 16 to 18 h post infection every 8 h for 2 days. Bacterial clearance from the lung tissue was assessed at 24 and 48 h post infection. CAZ-AVI and imipenem resulted in a 5 to 6 $\log_{10}$ reduction in bacterial load after 24 and 48 h (Figure 5).

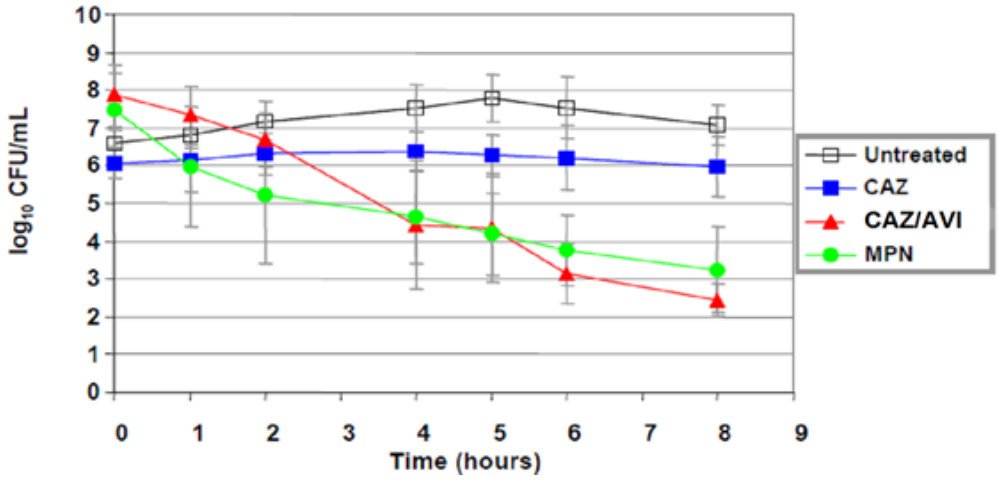
Figure 5. **Efficacy of CAZ-AVI Against AmpC and SHV-11 β-Lactamase-producing *K. pneumoniae* in a Mouse Pneumonia Infection Model**



4.2.1.4 Rabbit Meningitis

Rabbits were infected with AmpC β-lactamase-producing *K. pneumoniae* by inoculating 10^5 CFU into the subarachnoid space. Intravenous therapy was administered 8 h post infection with ceftazidime alone at 150 mg/kg or in combination with avibactam at 37.5 mg/kg (4:1 ratio) or meropenem at 125 mg/kg. Cerebrospinal fluid (CSF) was sampled over 8 h. The kinetics of avibactam in rabbit plasma and CSF were similar to ceftazidime and the mean penetration of avibactam into CSF was 38%. Ceftazidime monotherapy was unable to reduce the CSF bacterial load. Meropenem exhibited a mean killing rate of -4.2 $\log_{10}$ over 8 h. Co-administration of avibactam significantly protected the activity of ceftazidime resulting in a mean killing rate of > -5 $\log_{10}$ over 8 h for the combination regimen (Figure 6).

Figure 6. Changes in Bacterial Burden of *K. pneumoniae* (AmpC) in CSF Samples During Therapy with Ceftazidime, CAZ-AVI and Meropenem



4.2.2 Determination of PK/PD Targets from Nonclinical Studies

Much of the PK/PD information used in understanding the likely clinical antimicrobial efficacy of an antibiotic has been generated from in vitro models and animal models of infection (Ambrose et al, 2007). The percent of time that free-drug concentrations remain above the MIC over a dose interval (%*f*T > MIC) is well-established as the PK/PD index associated with the efficacy of β-lactams such as ceftazidime (Craig, 1995; Craig, 2003, Craig, 2007, Muller et al, 2013). The percent of time that free-drug concentrations are above a 'critical' or 'threshold' concentration (C_T) over a dose interval (%*f*T > C_T) was determined to be the PK/PD index associated with the efficacy of avibactam (Coleman et al, 2014; Berkhout et al, 2013a; Berkhout et al, 2013b, Study CAZ-AVI-M1-066).

4.2.2.1 PK/PD Target for Ceftazidime

Andes and Craig showed that approximately 30% *f*T > MIC of ceftazidime was related to bacteriostasis over 24 h for *Enterobacteriaceae* in the neutropenic mouse lung infection model, and a bactericidal effect of 2 to 3 $\log_{10}$ killing was achieved by roughly 50% *f*T > MIC (Andes and Craig, 2002). For *P. aeruginosa*, bacteriostasis was achieved in the neutropenic thigh infection model at about 40% *f*T > MIC of ceftazidime (Craig, 2003). Using clinical trial data, Muller *et al*. determined that exposures to ceftazidime predicted clinical and microbiological outcomes in patients with nosocomial pneumonia, with a %*f*T > MIC of ≥ 45% associated with a favorable outcome (Muller et al, 2013). Similarly, MacVane *et al*. showed that %*f*T>MIC > 53% was associated with microbiological success in patients with ventilator-associated bacterial pneumonia treated with ceftazidime or cefepime (MacVane et al, 2014). In addition, it has been shown in the neutropenic mouse thigh infection model that the pharmacodynamic target associated with efficacy of cephalosporins against ESBL-producing *Enterobacteriaciae* organisms is the same as that for non-ESBL-producing bacteria (50% T > MIC) (Andes and Craig, 2005). Taken together, the data above suggest that a PK/PD target of 40-50% *f*T>MIC for ceftazidime would be appropriate to use in PTA analyses for CAZ-AVI.

4.2.2.2 PK/PD Targets for Avibactam

The relevant PK/PD index for avibactam (%*f*T > C_T) was determined using both in vitro hollow fiber infection models and in vivo animal models of infection, with CAZ-R *Enterobacteriaceae* and *P. aeruginosa.*

4.2.2.2.1 Avibactam Target in Combination with Ceftazidime for Enterobacteriaceae

Coleman *et al*. conducted a series of experiments using the hollow fiber infection model with 8 CAZ-R *Enterobacteriaceae* strains to define the PK/PD target for avibactam (Coleman et al, 2014). The strains used were all clinical isolates with high ceftazidime MICs (≥ 64 mg/L) and a range of CAZ-AVI MICs (≤ 0.125 to 4 mg/L). They produced different β-lactamases (AmpC, CTX-M-15, SHV-5, SHV-1, TEM-1, TEM-10, KPC-3) and included a high level AmpC-producing isolate (*E. cloacae* 293HT96).

Continuous infusions of ceftazidime (8 or 16 mg/L) were studied in combination with avibactam concentrations that were varied to simulate single-dose human PK profiles. For all avibactam regimens studied, rapid killing of CAZ-R *Enterobacteriaceae* was observed with regrowth occurring between 12 and 24 h. The concentration of avibactam measured at the 12 h time point was therefore taken as the C_T of avibactam necessary to maintain growth suppression. Values of C_T determined in this manner ranged from 0.15 to 0.28 mg/L.

Additional hollow fiber studies were designed to determine the avibactam concentration associated with regrowth in the presence of ceftazidime concentrations that simulated the human PK profile for 1 or 2 g administered q8h. For these experiments, constant infusions of avibactam were given for 4.5 to 24 hours. In the presence of ceftazidime 2 g q8h, constant infusions of avibactam at a concentration of 0.25-0.5 mg/L for 4.5 hours (~half of proposed dosing interval) were required to suppress regrowth for 12-24 h. Based on these data, it was concluded that the avibactam concentration at the mid-point of an 8-h dosing interval should be between 0.25-0.5 mg/L for growth suppression (~50% $fT > C_T$ of 0.25-0.5 mg/L). These results demonstrate that a C_T of 0.5 mg/L avibactam is appropriate for estimating probability of target attainment for CAZ-AVI against *Enterobacteriaceae*.

When a single dose of CAZ-AVI simulating the proposed clinical dose (2 g ceftazidime + 0.5 g avibactam) was tested in the hollow fiber system, the combination was rapidly cidal against all 8 ceftazidime-resistant *Enterobacteriaceae* strains, and growth of all organisms was held below the limit of detection ($< 10^2$ CFU/mL) for the entire 8-h period of the experiment.

4.2.2.2.2 Avibactam Target in Combination with Ceftazidime for P. aeruginosa

Berkhout *et al*. conducted a series of experiments with CAZ-AVI in the neutropenic mouse thigh and lung infection models to elucidate the PK/PD target for avibactam against *P. aeruginosa* (Berkhout et al, 2013a and 2013b). Seven well-characterized CAZ-R *P. aeruginosa* strains obtained from a variety of clinical sources were used in these experiments. The ceftazidime MICs for these strains ranged from 32 to 128 mg/L, and the CAZ-AVI MICs ranged from 2 to 16 mg/L. Neutropenic mice were inoculated with approximately 10^6 CFU either intramuscularly (thigh infection) or intra-nasally (lung infection) to induce infection.

In each mouse infection model, the investigators first determined the dose of ceftazidime monotherapy for each bacterial strain that would just allow maximal growth (1-2 $\log_{10}$ of bacterial CFU/g growth after 24 hours). The objective was to use a ceftazidime dose at which any increase in antibacterial potency caused by inhibition of β-lactamases by avibactam would result in a decrease in bacterial counts. Full dose fractionation of avibactam was then conducted in the presence of this dose of ceftazidime.

The dose fractionation studies with both the thigh and lung infection models demonstrated that the PK/PD index for avibactam that was best-associated with efficacy was $\%fT > C_T$ for a C_T of 1 mg/L. In addition, it was shown in the lung infection model that the effect of avibactam was dependent on dose frequency, where a decreased effect was seen with decreased frequency. This further substantiates that the PK/PD target for avibactam is time-dependent.

A greater %*f*T > C_T was required in the thigh infection model than in the lung infection model. In the thigh infection model, the mean %*f*T > C_T for a C_T of 1 mg/L avibactam was 40.2% for bacterial stasis and 50.3% for 1-log kill. In the lung infection model, the mean %*f*T > C_T values for a C_T of 1 mg/L associated with stasis, 1-log kill, and 2-log kill were 20.2%, 24.0%, and 30.3%, respectively.

From these data, it was concluded that targets of 40% to 50% *f*T > C_T for a C_T of 1 mg/L avibactam would be appropriate for estimating PK/PD target attainment against *P. aeruginosa*. The similar magnitude of the target %*f*T > MIC for ceftazidime and %*f*T > C_T for avibactam suggests that concentrations of the inhibitor should exceed the C_T for about the same period of time that concentrations of the β-lactam are above the MIC.

4.2.3 Animal Models of Infection using Human-simulated Pharmacokinetics

In addition to the in vivo animal models of infection described above, a series of studies were conducted using dosing regimens to achieve free drug concentration-time profiles in animals that approximate those in humans given 2 g ceftazidime q8h (2-h infusion), with or without avibactam at 0.5 g q8h (2-h infusion). The PK/PD target attainment analyses that led to selection of the proposed CAZ-AVI dose regimen of 2.5 g q8h as a 2-h infusion are summarized in Section 4.4.

4.2.3.1 Murine Neutropenic Thigh Infection Model

Crandon *et al*. evaluated the efficacy of CAZ-AVI in the murine thigh infection model against 27 isolates of *P. aeruginosa* with ceftazidime MICs ranging from 8 to 128 mg/L and CAZ-AVI MICs ranging from 4 to 32 mg/L (Crandon et al, 2012). The free drug-concentration time profile seen in humans given 2 g ceftazidime q8h (2-h infusion), with or without avibactam at 0.5 g q8h (2-h infusion) was studied. The animals were treated with ceftazidime or CAZ-AVI 2 h post infection and the change in bacterial burden in the thigh was determined after 24 h and compared with the 0-h controls.

The human simulated regimen produced predictable efficacy (based on MIC), with bacterial killing (0.7- to > 3-log reductions in bacterial counts) against 16 of 17 isolates with CAZ-AVI MICs that were ≤ 8 mg/L and 5 of 8 isolates with CAZ-AVI MICs of 16 mg/L. Two isolates with CAZ-AVI MIC values of 32 mg/L were also studied. One isolate responded with a 1-$\log_{10}$ reduction in titer and the other resulted in net stasis. After the 24-h treatment period with CAZ-AVI, no bacterial colonies were observed from thigh homogenates plated on drug-containing plates, suggesting that there was no resistance development.

In a second study by the same investigators, the efficacy of CAZ-AVI against *Enterobacteriaceae* with MIC values ≥ 8 mg/L was evaluated. For 2 of the isolates, the β-lactamase genotype was known by genomic sequencing (*K. pneumoniae* KP 496 bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1} truncated bla_{OXA-9}; and *Providencia stuartii* PS 58 bla_{ACC-4}, bla_{TEM-1}). Additional isolates were added against which the CAZ-AVI MIC was ≥128 mg/L but for which the genotype was unknown. The simulated human exposures of CAZ-AVI 2.5 g q8h (2-h infusion) resulted in decreases in CFU against 13 of 14 *Enterobacteriaceae* with CAZ-AVI MICs ≤ 16 mg/L. The remaining isolate was an *E. cloacae* (MIC ceftazidime > 128 mg/L; MIC CAZ-AVI 8 mg/L), with a static response to CAZ-AVI. Variable activity was noted at CAZ-AVI MICs of 32 mg/L and efficacy, which was unexpected given 0% *f*T > MIC, was observed against isolates with CAZ-AVI MIC values ≥ 128 mg/L.

4.2.3.2 Murine Pneumonia Model

The effect of simulated human CAZ-AVI PK on 28 *P. aeruginosa* isolates in a neutropenic mouse lung infection model was also studied (Housman et al, 2014). CAZ-AVI demonstrated 1- to 4–log reductions in bacterial titers over 24 h against 26 of 27 *P. aeruginosa* isolates that tested with MIC values of ≤ 32 mg/L. The 1 exception was an isolate with a CAZ-AVI MIC of 16 mg/L. Activity was also not observed against the 1 isolate with a CAZ-AVI MIC of 64 mg/L. Similarly, simulated human PK of ceftazidime alone resulted in 0.5- to 2-log reductions in bacterial titers over 24 h against isolates that tested with ceftazidime MICs of 32 or 64 mg/L. The median PK profile used in these experiments provided 34% *f*T > 32 mg/L, and 6% *f*T > 64 mg/L. The approximated median human exposure of ceftazidime was less effective against isolates for which the ceftazidime MIC was 128 mg/L where 1 of 3 isolates responded with an approximately 1.5 -log reduction in count, and the other 2 responded with stasis.

4.3 CAZ-AVI CLINICAL PHARMACOLOGY

4.3.1 Pharmacokinetics

The CAZ-AVI Clinical Pharmacology program focused on defining the PK of avibactam alone and in combination with ceftazidime. As part of the CAZ-AVI development program, the PK of avibactam has been investigated in 10 Phase 1 Clinical Pharmacology studies after administration of avibactam or CAZ-AVI by IV infusion. Seven of these Phase 1 studies also provided PK data for ceftazidime. The studies in healthy subjects included young adult subjects, male and female subjects, subjects ≥ 65 years of age, and Japanese subjects. Avibactam was administered as single IV infusions of 50 to 2000 mg or multiple IV infusions of 500 to 1000 mg q8h for up to 10 days. The PK of avibactam was also studied following administration of a single dose to subjects with mild, moderate, and severe renal impairment, and ESRD (on and off hemodialysis). In addition, the PK of avibactam was studied following administration of [^{14}C]-avibactam to healthy male subjects, and one study explored the distribution of ceftazidime and avibactam in bronchial ELF and plasma after repeated doses of CAZ-AVI. The DDI potential was investigated between ceftazidime and avibactam, and between CAZ-AVI and MTZ. The effect of a supratherapeutic dose of CAZ-AVI on the QTc interval was also evaluated in healthy subjects. Sparse plasma samples were collected for PK analyses in 2 Phase 2 studies, 1 in subjects with cUTI and 1 in subjects with cIAI, for population PK analysis.

Avibactam PK data from 4 Phase 1 studies in the CXL development program were included in the 505(b)(2) NDA for CAZ-AVI. The CXL studies investigated the PK of avibactam following administration in combination with ceftaroline fosamil in healthy subjects, after repeated dosing of CXL in subjects with severe renal impairment, and after a single dose of CXL in subjects with augmented renal clearance (ARC) and sepsis. The impact of obesity on the PK of avibactam was also investigated following a single dose of CXL.

A Phase 1 study demonstrated that there was no PK interaction between ceftazidime and avibactam after single or multiple doses, thus validating the use of PK data from studies with avibactam alone or ceftazidime alone. Similarly, there was no PK interaction between ceftaroline and avibactam, which supports the use of avibactam PK data from the CXL studies in defining the PK profile of avibactam.

Table 22 summarizes mean PK parameters for ceftazidime and avibactam in healthy adult male subjects with normal renal function after single and multiple dose administration of CAZ-AVI (2 g/0.5 g) every 8 h.

Table 22. Pharmacokinetic Parameters (Geometric Mean [%CV]) of Ceftazidime and Avibactam in Healthy Adult Male Subjects

Parameter	Ceftazidime		Avibactam	
	Single Dose[a], 2-h Infusion (n = 16)	Multi-dose[a], 2-h Infusions q8h for 11 Days (n = 16)	Single Dose[a], 2-h Infusion (n = 16)	Multi-dose[a], 2-h Infusions q8h for 11 Days (n = 16)
C_{max} (mg/L)	88.1 (14)	90.4 (16)	15.2 (14)	14.6 (17)
T_{max} (h)[b]	2.00 (2.00-2.02)	2.00 (1.50-2.02)	2.00 (2.00-2.02)	2.00 (2.00-2.02)
AUC (mg-h/L)[c]	289 (15)[d]	291 (15)	42.1 (16)[e]	38.2 (19)
$T_{1/2}$ (h)	3.27 (33)[d]	2.76 (7)	2.22 (31)[e]	2.71 (25)
CL (L/h)	6.93 (15)[d]	6.86 (15)	11.9 (16)[e]	13.1 (19)
V_{ss} (L)	18.1 (20)[d]	17.0 (16)	23.2 (23)[e]	22.2 (18)

Abbreviations: AUC = area under plasma concentration-time curve; CL = apparent total body clearance of drug from plasma; C_{max} = maximum plasma drug concentration; q8h = every 8 h; T_{max} = time of C_{max}; $T_{1/2}$ = terminal elimination half-life; V_{ss} (L) = volume of distribution at steady state.

a 2 g ceftazidime + 0.5 g avibactam.

b Reported as median (range).

c $AUC_{0\text{-}inf}$ reported for single-dose administration; $AUC_{0\text{-}tau}$ reported for multiple-dose administration.

d n = 15.

e n = 13.

Key findings from the clinical pharmacology studies and nonclinical drug metabolism and PK studies are summarized below:

- The C_{max} and AUC of ceftazidime increase directly with dose (FORTAZ package insert, 2010). Avibactam demonstrated linear pharmacokinetics across the dose range studied (50 mg to 2000 mg) for single IV administration.

- The time to C_{max} (T_{max}) of ceftazidime and avibactam generally occurs near the end of the infusion. No time-dependent PK changes were observed for ceftazidime or avibactam after repeated doses.

- The volume of distribution of both ceftazidime and avibactam in healthy subjects approximates extracellular fluid volume. The mean volume of distribution at steady state (V_{ss}) for ceftazidime ranged from 17.0 to 28.2 L in the CAZ-AVI Phase 1 studies, and the V_{ss} of avibactam ranged from 15.2 to 24.4 L.

- Little or no biotransformation of avibactam occurred in human liver microsomes, indicating no CYP-dependent metabolism. Following IV infusion of 500 mg [^{14}C]- avibactam, unchanged avibactam was the major drug-related component in both human plasma and urine, with > 95% of the administered radioactivity recovered from urine within 12 h of dosing. Ceftazidime also undergoes little or no metabolism and is eliminated almost entirely as unchanged drug in the urine (FORTAZ package insert, 2010).

- Avibactam at clinically relevant concentrations does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 in vitro in human liver microsomes. Avibactam and ceftazidime showed no in vitro CYP induction potential within the clinically relevant exposure range

- The $T_{½}$ of ceftazidime is approximately 1.9 h following IV administration (FORTAZ package insert, 2010). The $T_{½}$ of avibactam following IV infusion is approximately 2 h and was similar across the studied doses.

- There is no appreciable accumulation of ceftazidime or avibactam following multiple IV infusions (2 g ceftazidime and 0.5 g avibactam) administered every 8 h for up to 11 days in healthy adults with normal renal function.

- The clearance of avibactam (after a single 100-mg dose) is significantly decreased in subjects with mild (2.6-fold), moderate (3.8-fold), and severe renal impairment (7.1-fold) and those with ESRD (off dialysis) (15-fold), as compared to subjects with normal renal function. The $T_{½}$ is significantly prolonged in subjects with impaired renal function, necessitating dosage adjustment of CAZ-AVI for those with estimated CrCL $\leq$ 50 mL/min.

- Both ceftazidime (FORTAZ package insert, 2010) and avibactam are hemodialyzable (55% of avibactam dose was removed during a 4-h session); CAZ-AVI should be administered after hemodialysis on days when patients receive CAZ-AVI and hemodialysis treatment.

- No dose adjustment is needed for CAZ-AVI based on age or gender or in patients with impaired hepatic function

- Neither ceftazidime nor avibactam was found to be an inhibitor of the following hepatic and renal transporters in vitro at clinically relevant concentrations: MDR1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, MRP4, OCT1 and OCT2. Avibactam was not a substrate of MDR1, BCRP, MRP4, or OCT2, but was a substrate of human OAT1 and OAT3 kidney transporters

- Binding of avibactam (5.7% – 8.2%) and ceftazidime (5% – 23%) to human plasma proteins is low and independent of concentration.

The potential for DDI with CAZ-AVI is low based on the following: both ceftazidime and avibactam undergo limited metabolism; avibactam showed no significant inhibition or induction of CYP enzymes in vitro, and ceftazidime also showed no CYP induction potential; both avibactam and ceftazidime have low binding to human plasma proteins; and, avibactam and ceftazidime did not inhibit any major renal or hepatic transporters in vitro in the clinically relevant exposure range. Avibactam was shown to be a substrate of human OAT1 and OAT3 in vitro, which may contribute to its active secretion by the kidneys. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited (by 56% to 70%) by probenecid, a potent OAT inhibitor. The clinical impact of potent OAT inhibitors on the PK of avibactam is not known. It was demonstrated in Phase 1 studies that there was no PK interaction between ceftazidime and avibactam, and no PK interaction between ceftaroline fosamil and avibactam. In addition, a Phase 1 study showed no PK interaction between CAZ-AVI and MTZ, supporting the concomitant use of MTZ in cIAI subjects.

A Phase 1 study was conducted with CAZ-AVI in healthy adult subjects to evaluate penetration of ceftazidime and avibactam into the lungs. This study demonstrated that the penetration of avibactam into ELF was similar to that of ceftazidime. Following administration of CAZ-AVI 2.5 g (2 g ceftazidime and 0.5 g avibactam) or 3 g ceftazidime and 1 g avibactam to healthy male subjects every 8 h as a 2 h infusion for 3 days, the C_{max} and area under the plasma concentration-time curve from time 0 to time of last measurable concentration ($AUC_{0-\tau}$) values of avibactam in ELF were 28% to 35% and 32% to 35% of the plasma C_{max} and $AUC_{0-\tau}$, respectively. The C_{max} and $AUC_{0-\tau}$ values of ceftazidime in ELF were approximately 23% to 26% and 31% to 32% of the plasma C_{max} and $AUC_{0-\tau}$, respectively. In addition, the elimination patterns were similar between ELF and plasma for each drug.

Population PK

Data from the completed Phase 1 and Phase 2 studies were used to develop population PK models for avibactam and ceftazidime. The population PK dataset for avibactam included 8124 observations from 475 subjects from 12 clinical studies. For ceftazidime, the PK dataset included 3617 observations from 216 subjects from 6 clinical studies.

While the dataset for avibactam included a total of 33 subjects from dedicated Phase 1 studies of the effects of renal impairment, there were no subjects in the ceftazidime dataset from such studies. In the Phase 2 program, only 4 subjects were recorded as having moderate renal impairment based on the Cockcroft-Gault-derived CrCL at baseline. Therefore, due to the scarcity of subjects with moderate or severe renal function in the ceftazidime dataset, historical literature data for ceftazidime in patients with renal impairment was used to augment the population PK model to determine the relationship

between clearance (CL) and CrCL for patients with CrCL < 50 mL/min (Ackerman et al, 1984; Leroy et al, 1984; Welage et al, 1984).

Two-compartment models with first-order elimination from a central compartment were found to adequately describe the population PK of both avibactam and ceftazidime. Covariate analyses demonstrated that the main predictor of CL for both avibactam and ceftazidime was CrCL. For apparent volume of distribution of the central or plasma compartment (V_1), the main predictor for both compounds was total body weight for both compounds. The Phase 2 subject population (cIAI and cUTI) was also identified as a significant covariate, independent of any underlying differences in CrCL and/or body weight between the Phase 2 subject populations and Phase 1 subjects. Compared with Phase 1 subjects, increased CL was associated with the cIAI population for both compounds, and increased V_1 was associated with the cIAI and cUTI populations for both compounds. Increased volume of distribution and faster clearance have been reported for β-lactam antibiotics in patients with intra-abdominal infection or previous abdominal surgery, and may be related to physiological changes in these patients such as development of abscesses, perforation, or ischemia of the bowel as well as intra-abdominal hypertension (Adnan et al, 2012).

These models were used to explore possible PK/PD relationships in the Phase 2 studies and to conduct Monte Carlo simulations to evaluate the PTA for ceftazidime and avibactam at the proposed dose (Section 4.4).

4.3.2 Effect on Cardiac Repolarization

The effect of avibactam on QT/QTc interval was evaluated pre-clinically and showed minimal potential for QT/QTc prolongation. A Phase 1, 4-way, crossover thorough QT study (Study D4280C00007) investigated the QT effects of a single supratherapeutic dose of ceftazidime (3 g) plus avibactam (2 g), administered as a 30-minute infusion. Results demonstrated that CAZ-AVI did not significantly prolong the QTc interval. Across evaluation time points, the largest 90% upper bound for the placebo-corrected mean change from baseline (ΔΔQTcF) was 5.9 msec. There were no QTcF intervals > 450 msec and no QTcF interval changes from baseline > 30 msec. PK parameters for ceftazidime and avibactam confirmed supratherapeutic exposures at the doses administered. Additionally, assay sensitivity was confirmed with an oral 400 mg moxifloxacin dose (ie, lower limit of the 2-sided 90% CI for mean ΔΔQTcF over the interval of 1 to 4 h > 5 msec).

4.4 CAZ-AVI PK/PD TARGET ATTAINMENT ANALYSES

4.4.1 PK/PD Target Attainment Analyses to Support Proposed Dose

The population PK models for ceftazidime and avibactam described above were used to explore PK/PD relationships in the Phase 2 studies and to conduct simulations to evaluate the probability of joint PK/PD target attainment for ceftazidime and avibactam. The PTA analyses were used to support proposed breakpoints and to justify the proposed marketed dose with dose adjustments for renal impairment.

An exposure-response relationship could not be established using clinical data from cIAI and cUTI Phase 2 studies due to the limited exposure range in these studies. In both Phase 2 studies, more than 80% of subjects met the pre-specified joint PK/PD target (defined below), regardless of whether they had a "favorable" or "unfavorable" overall microbiological response. Furthermore, nearly all subjects were clustered near the high range (ie, well over 50%) of %*f*T > MIC for ceftazidime (using the CAZ-AVI MIC) and %*f*T > C_T for avibactam. Therefore, identification of PK/PD targets from the clinical data was not feasible, and CAZ-AVI dose selection was based on PK/PD targets from nonclinical microbiological data.

As described in Section 4.2.2, the PK/PD targets associated with efficacy of CAZ-AVI have been shown to be %*f*T > MIC and %*f*T > C_T for ceftazidime and avibactam, respectively. These targets from the nonclinical studies were used in simulations to assess the PTA. Four joint PK/PD targets were evaluated, with the most conservative target being 50% *f*T > CAZ-AVI MIC for ceftazidime and 50% *f*T > C_T of 1 mg/L for avibactam. As discussed above, these target parameters provide coverage of the higher exposures required for *P. aeruginosa* isolates; exposure targets of 40-50% *f*T > CAZ-AVI MIC for ceftazidime and 40-50% *f*T > C_T of 0.5 mg/L would be adequate for *Enterobacteriaceae*.

The population PK models for ceftazidime and avibactam were used to conduct Monte Carlo simulations to determine the probability of PK/PD target attainment to support CAZ-AVI dose selection for subjects across 6 different levels of renal function, spanning from normal renal function to ESRD (FORTAZ® package insert, 2010). The dose regimens simulated were based on the dose adjustments by renal function for ceftazidime in the US FORTAZ label (FORTAZ® package insert, 2010), with the avibactam dose adjusted to maintain the CAZ-AVI dose ratio at 4:1. Demographic covariates and CrCL for 5000 theoretical subjects were simulated for each renal function group. Because subjects with cIAI showed lower exposures than healthy subjects and subjects with cUTI, the cIAI population was used to simulate exposures and calculate associated target attainment.

For the simulation of subjects with normal renal function, the demographics for the simulation were bootstrapped from the observed weight and CrCL values in the cIAI Phase 2 study. For the simulation of subjects in each of the reduced renal function

categories, the same bootstrapped distribution of weight was chosen as a conservative assumption, while for CrCL, a uniform distribution was used within each sub-category. PK/PD target attainment was calculated as the percentage of the simulated subjects who met the PK/PD targets for both ceftazidime and avibactam simultaneously (referred to as joint PK/PD target attainment).

The following 4 joint PK/PD targets were evaluated:

- T1: 40% *f*T > MIC for ceftazidime and 40% *f*T > C_T of 0.5 mg/L for avibactam
- T2: 50% *f*T > MIC for ceftazidime and 50% *f*T > C_T of 0.5 mg/L for avibactam
- T3: 40% *f*T > MIC for ceftazidime and 40% *f*T > C_T of 1.0 mg/L for avibactam
- T4: 50% *f*T > MIC for ceftazidime and 50% *f*T > C_T of 1.0 mg/L for avibactam

The percent free fraction used to calculate free drug concentrations was 85% for ceftazidime and 92% for avibactam.

The target attainment results demonstrate that the proposed dose regimen for CAZ-AVI of 2.5 g (2 g ceftazidime + 0.5 g avibactam) given as a 2-h IV infusion q8h for subjects with normal renal function produces adequate target attainment for the most conservative joint PK/PD target of 50% *f*T > MIC at a CAZ-AVI MIC of 8 mg/L for ceftazidime and 50% *f*T > C_T for a C_T of 1 mg/L for avibactam (Table 23). The target attainment simulations therefore support a PK/PD "susceptible" breakpoint of ≤ 8 mg/L.

Table 23. Percentage of Simulated Patients with cIAI and Normal Renal Function Achieving Pre-Specified PK/PD Targets with 2.5 g CAZ-AVI Infused Over 2 h IV q8h by MIC

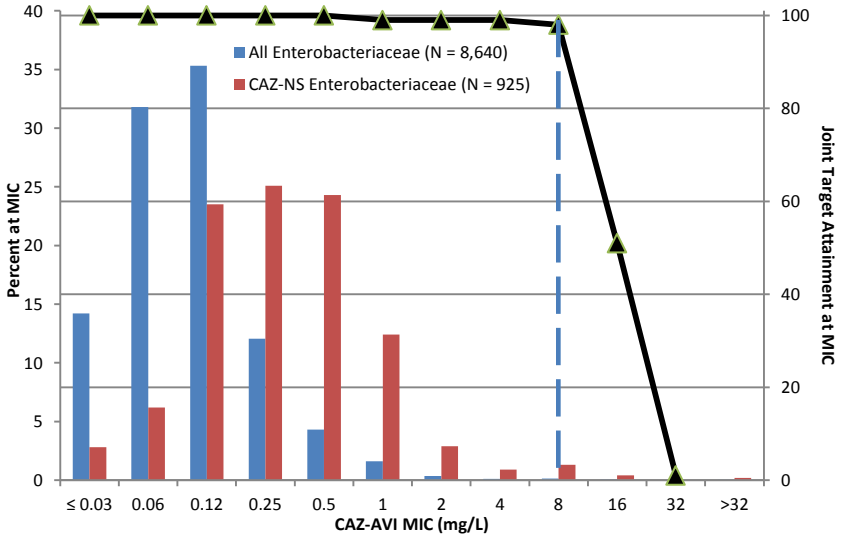
CAZ-AVI MIC (mg/L)	***PK/PD Target Definition***			
	***40% fT> MIC; 40% f*T > C_T, C_T = 0.5 mg/L**	***50% fT> MIC; 50% f*T > C_T, C_T = 0.5 mg/L**	***40% fT> MIC; 40% f*T > C_T, C_T = 1 mg/L**	***50% fT> MIC; 50% f*T > C_T, C_T = 1 mg/L**
2	100	100	100	98.9
4	100	100	100	98.9
8	99.8	98.3	99.8	98.1
16	75.4	50.8	75.4	50.8
32	5.1	1.3	5.1	1.3

Figure 7 shows the percentage of simulated cIAI subjects that achieve joint PK/PD targets overlaid on histograms of MIC distributions for *Enterobacteriaceae* and *P. aeruginosa*. These results demonstrate that the proposed CAZ-AVI dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h infused over 2 h will provide adequate exposures to cover the most likely pathogens to be encountered among serious infections in the clinical setting based on analysis of extensive surveillance data.

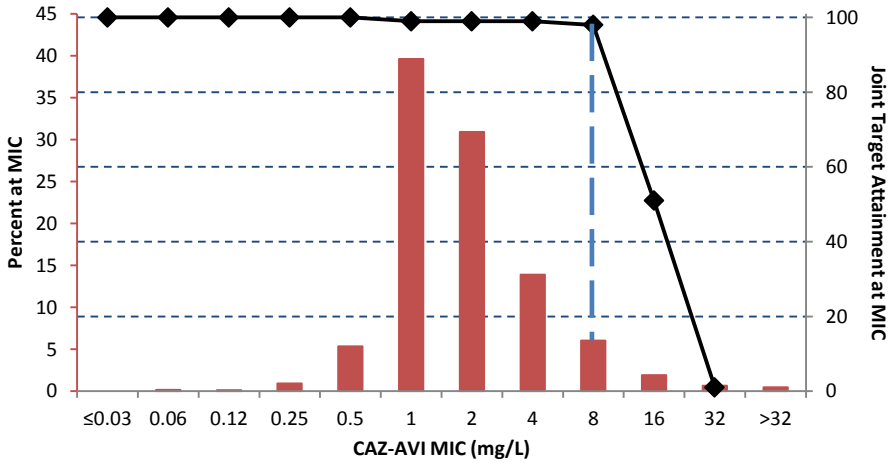
For completeness, simulations were also conducted for cUTI subjects. Simulated exposures were higher in cUTI subjects than cIAI, based on the population-related differences in population PK model estimates. Although this increased some of the joint PTA results above 90% for additional renal function categories at 16 mg/L, the combined results for joint PTA for cUTI across all renal categories supported a PK/PD breakpoint of 8 mg/L.

Figure 7. Percentage of Simulated cIAI Patients Achieving Joint PK/PD Target Attainment Following IV Administration of Proposed CAZ-AVI Dose Overlaid on a Histogram of MIC Distributions for *Enterobacteriaceae* (A) and *Pseudomonas aeruginosa* (B)

A. *Enterobacteriaceae*



B. *Pseudomonas aeruginosa*



Simulations for subjects with normal renal function achieving 50% *f* T>MIC for ceftazidime and 50% *f* $T>C_T$ of 1 mg/l avibactam following IV administration of 2000 mg ceftazidime/500 mg avibactam q8h by 2 h infusion.

4.4.1.1 Use in Infections with Limited Treatment Options

The limited use indication for HABP/VABP caused by aerobic Gram-negative infections where limited or no alternative therapies are available is supported by the long history of use of ceftazidime in HABP/VABP patients, the ELF study with CAZ-AVI, nonclinical animal models of infection demonstrating the efficacy of CAZ-AVI against CAZ-R *P. aeruginosa*, and the target attainment simulations for cIAI subjects.

The ELF study demonstrated that ceftazidime and avibactam are able to penetrate into ELF to a similar extent and with similar kinetics. The exposure of both drugs in the lung was approximately 30-35% of the exposure in plasma. The penetration of ceftazidime and avibactam into the ELF of mice following administration of CAZ-AVI was shown to be slightly less (approximately 25%) than the 30–35% ELF penetration observed in humans (Berkhout et al., 2013c). The use of PK/PD targets derived from plasma levels in the neutropenic mouse lung infection model in target attainment analyses would therefore be a conservative approach for estimating the efficacy of CAZ-AVI in humans for respiratory infections. In addition, CAZ-AVI demonstrated efficacy against CAZ-R *P. aeruginosa* in both the neutropenic mouse lung infection and thigh infection models (Section 4.2.2.2.2), and the %$fT>C_T$ for avibactam associated with efficacy in the lung infection model was less than the %$fT>C_T$ associated with efficacy in the thigh infection model.

The PK/PD target for ceftazidime used in the PTA simulations (50% fT > CAZ-AVI MIC) is consistent with recent work showing that %fT>MIC greater than 45% for ceftazidime was associated with favorable clinical and microbiological outcomes in patients with nosocomial pneumonia caused by Gram-negative pathogens (Muller et al, 2013), and %fT>MIC > 53% was associated with microbiological success in patients with VABP treated with ceftazidime or cefepime (MacVane et al, 2014). The avibactam target of 50% $fT > C_T$ of 1 mg/L is based on the murine thigh infection model with CAZ-R *P. aeruginosa*, which as noted in Section 4.2.2.2.2, required a higher % $fT > C_T$ than the lung infection model.

Dose selection was based on target attainment simulations for cIAI subjects, who were predicted to have faster clearance, and lower plasma levels, of both ceftazidime and avibactam compared to cUTI subjects or healthy subjects. Although patients with HABP/VABP have been reported to have faster clearance of β-lactams than other patient populations, potentially as a result of augmented renal clearance and other factors (Roberts and Lipman, 2013), the estimated clearance of ceftazidime for cIAI subjects from the population PK model (11.3 L/h) is greater than the estimate for ceftazidime clearance in nosocomial pneumonia patients (6.47 L/h) reported by Muller *et al*. (2013). Based on this observation, target attainment in HABP/VABP patients would be expected to be at least as good as target attainment in the simulated cIAI patients.

4.5 CAZ-AVI EFFICACY IN HUMANS

For the 505(b)(2) NDA, the efficacy of CAZ-AVI was based in part on the efficacy of ceftazidime alone from publically available information. As described above, ceftazidime alone has been an effective antibacterial agent for the treatment of serious bacterial infections for almost 3 decades, and its efficacy specific to cIAI and cUTI caused by CAZ-S pathogens was supported by a systematic review of the literature and meta-analysis (Section 3.0).

In Section 4.5.1 and Section 4.5.2 below, the efficacy of CAZ-AVI is described in the context of proof-of-concept Phase 2 cIAI and cUTI studies, respectively. These small Phase 2 studies were descriptive in nature and not powered for inferential statistics or non-inferiority. They enrolled subjects with infections caused predominantly by CAZ-S pathogens. The results revealed that the efficacy of CAZ-AVI was similar to the historical efficacy associated with ceftazidime alone. The data demonstrate that both CAZ-AVI and ceftazidime alone remain efficacious in the treatment of cIAI and cUTI caused by CAZ-S pathogens.

In addition, we have demonstrated that avibactam extends the activity of ceftazidime against CAZ-NS pathogens in human infections. The efficacy of CAZ-AVI in the treatment of cIAI and cUTI caused by CAZ-NS pathogens is detailed in Section 4.5.3, which includes subjects infected by CAZ-NS pathogens from the Phase 2 cIAI and cUTI studies, as well as interim data from the ongoing Resistant Pathogen study. The data reveal that CAZ-AVI is associated with similar or numerically higher success rates than carbapenem-based comparator regimens in the treatment of cIAI and cUTI caused by CAZ-NS pathogens.

4.5.1 Phase 2 cIAI Study (NXL104/2002)

4.5.1.1 Study Methodology

Study Design

Study NXL104/2002 was a Phase 2, descriptive, multinational, randomized, double-blind, active-controlled study of adult subjects with cIAI. Subjects were stratified by baseline severity of disease (APACHE II score ≤ 10, and > 10 to ≤ 25) and randomized 1:1 to either CAZ-AVI plus MTZ or to meropenem.

The study enrolled subjects from the US, Bulgaria, France, Poland, Romania, the Russian Federation, India, and Lebanon. These countries were selected to enrich for enrollment of subjects with infections caused by CAZ-NS (eg, ESBL-producing) pathogens.

The dosage of CAZ-AVI was 2.5 g (2.0 g ceftazidime + 0.5 g avibactam) administered q8h as a 30-minute IV infusion. Metronidazole (0.5 g IV q8h) was added to CAZ-AVI to provide empiric coverage for anaerobic organisms. Meropenem (1 g IV q8h) was selected

as the active comparator based on its efficacy against Gram-negative (including ESBL-producing strains) and anaerobic pathogens isolated commonly in cIAI, and it is FDA-approved and widely used for cIAI treatment (MERREM® package insert, 2013). Concomitant use of antibiotics with coverage limited to Gram-positive pathogens was permitted in subjects for whom MRSA or enterococci were suspected or documented pathogens causing infection.

The expected duration of treatment was 5 to 14 days. After at least 5 days of therapy, the investigator could discontinue study drug if the subject had improved clinically, as evidenced by (1) white blood cell (WBC) count < 12,500/µL, (2) maximum oral temperature < 38°C during the preceding 24 h in the absence of antipyretics or corticosteroids, (3) significant improvement of abdominal signs and symptoms, (4) return of bowel function and restoration of oral intake, and (5) no requirement of further antibiotic therapy.

The study was designed to enroll a subject population that was consistent with the FDA Guidance for Industry for cIAI at the time of study initiation. Key inclusion criteria included: age 18 to 90 years; cIAI meeting specific criteria (eg, diagnosis of cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall, diverticulitis with perforation or abscess, appendiceal perforation or periappendiceal abscess, gastrointestinal perforations, intra-abdominal abscesses, and secondary peritonitis); evidence of systemic inflammatory response; physical exam findings consistent with cIAI; supportive radiographic imaging findings; and requirement for surgical intervention. Of note, infections limited to the hollow viscus (eg, simple cholecystitis and simple appendicitis) were not eligible, nor was spontaneous bacterial peritonitis associated with chronic ascites. Other key exclusion criteria included APACHE II score > 25; receipt of prior systemic antibacterial agents within the previous 72 h (except for ≤ 24 h of preoperative and/or postoperative antibiotic therapy or documented failure of prior antibiotic); estimated CrCL < 50 mL/min; and evidence of abnormal liver function (eg, ALT, AST, and bilirubin > 3 times the upper limit of normal [ULN]).

Determination of Clinical & Microbiological Responses

An overall clinical assessment (including signs/symptoms of infection and cultures from intra-abdominal site of infection and blood), vital signs, and detailed abdominal assessment were performed at baseline, daily during study therapy, at the discontinuation of study therapy, at the early follow-up or TOC visit 2 weeks after the last dose of study drug, and at LFU 4 to 6 weeks after the last dose of study drug. Microbiological assessments including Gram stain, WBC count, and culture were performed on specimens obtained from the intra-abdominal cavity or from the blood at baseline and as appropriate during the course of the study.

Clinical cure was defined as complete resolution or significant improvement of signs and symptoms of the index infection, and no further antimicrobial therapy or surgical or radiological intervention is necessary. Clinical failure was defined as death related to cIAI at any time point, documented persistent or recurrent cIAI, postsurgical open wound infections, or receipt of additional antibiotics for ongoing symptoms of cIAI.

Microbiological response was determined for each baseline pathogen isolated from intra-abdominal sites and/or blood at EOIV, TOC, and LFU visits.

Primary & Secondary Outcomes

The primary efficacy outcome is the clinical cure rate at TOC. The protocol-defined primary analysis was determined from the ME Population; however, in consultation with the FDA, the mMITT Population was used for the primary analysis in this submission.

The mMITT Population was defined as all randomized subjects who received at least 1 dose of study drug and met the disease definition of cIAI and had at least 1 bacterial pathogen identified at study entry regardless of susceptibility.

Secondary efficacy outcomes presented in this Briefing Document include: clinical response at EOIV and LFU in the mMITT Population and clinical response by baseline pathogen in the mMITT Population.

Statistical Analyses

This descriptive Phase 2 study was not statistically powered to demonstrate non-inferiority to the comparator. The 95% CIs for the proportions of subjects with clinical cure were determined using the Clopper-Pearson method, and the 95% CIs for the differences between treatment groups were determined using the non-stratified Miettinen-Nurminen method or the 2-sided test for proportions with continuity correction.

The protocol and Statistical Analysis Plan (SAP) stated that the determination of evaluable subject populations and outcomes would be based on investigator assessments. However, during blinded data review, it was determined that the investigator did not strictly apply the protocol-specified criteria for favorable response for a few subjects, with their response classified as indeterminate rather than failure. Efficacy results presented in this Briefing Document are based on the Sponsor's blinded review (ie, "Sponsor-verified"), with favorable response defined by the pre-specified criteria. Accordingly, the outcome for some subjects is reported more conservatively as failure rather than indeterminate.

4.5.1.2 Subject Disposition

Overall, 102 subjects were randomized into each treatment group; one subject in the CAZ-AVI + MTZ group did not receive a dose of study drug (Table 24). Most treated subjects completed study drug therapy. The most common reasons for discontinuation of study drug were adverse events and SAEs.

Table 24. Subject Disposition – Safety Population, Study NXL104/2002 (cIAI)

	CAZ-AVI + MTZ	***Meropenem***
Randomized	102	102
Received a Dose of Study Drug	101 (99%)	102 (100%)
Completed Therapy	93 (92.1)	95 (93.1)
Prematurely Discontinued Study Drug	8 (7.9)	7 (6.9)
Discontinued due to adverse event	4 (4.0)	1 (1.0)
Discontinued due to SAE	2 (2.0)	3 (2.9)
Investigator decision	1 (1.0)	0
Protocol deviation	1 (1.0)	0
Lost to follow up	0	2 (2.0)
Other	0	1 (1.0)
Completed study	91 (90.1)	96 (94.1)

Abbreviations: MTZ = metronidazole; SAE = serious adverse event.

a Percentages are calculated using the number of treated subjects in the Safety Population as the denominator.

A total of 203 subjects were included in the Safety Population and 174 were included in the mMITT Population (Table 25).

Table 25. Subject Evaluability for Analysis Populations (cIAI)

Study Population	***CAZ-AVI + MTZ N = 102***	***Meropenem N = 102***	***Total N = 204***
Randomized	102 (100.0)	102 (100.0)	204 (100.0)
Safety Population	101 (99.0)	102 (100.0)	203 (99.5)
mMITT Population	85 (83.3)	89 (87.3)	174 (85.3)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole.

Subjects were randomized in 8 countries, with enrollment by country generally balanced between the 2 treatment groups for subjects in the mMITT Population (Table 26).

Table 26. Subjects Entered into Study by Country and Treatment Group – mMITT Population, Study NXL104/2002 (cIAI)

Country	*CAZ-AVI + MTZ N = 85 n (%)*	*Meropenem N = 89 n (%)*	*Total N = 174 n (%)*
USA	9 (10.6)	5 (5.6)	14 (8.0)
Bulgaria	4 (4.7)	9 (10.1)	13 (7.5)
France	3 (3.5)	0 (0.0)	3 (1.7)
Poland	1 (1.2)	0 (0.0)	1 (0.6)
Romania	23 (27.1)	32 (36.0)	55 (31.6)
Russian Federation	9 (10.6)	13 (14.6)	22 (12.6)
India	34 (40.0)	30 (33.7)	64 (36.8)
Lebanon	2 (2.4)	0 (0.0)	2 (1.1)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole.

4.5.1.3 Subject Demographic and Baseline Characteristics

The treatment groups were balanced based on demographic and other baseline characteristics (Table 27). The majority of subjects was male, white, and had APACHE II scores ≤ 10.

Overall, the types and sites of infection and operative procedures were similar between treatment groups (Table 28). Nearly all subjects had pre-operative infections and the majority (90%) underwent open laparotomy as the initial surgical intervention. Subjects most commonly had general peritonitis (44.8% of all subjects). These baseline characteristics are similar to those reported among subjects enrolled in recent Phase 3 cIAI studies.

Table 27. Demographic and Baseline Characteristics – mMITT Population, Study NXL104/2002 (cIAI)

	CAZ-AVI + MTZ (N = 85)	***Meropenem (N = 89)***	***Total (N = 174)***
Gender, n (%) [a]			
Male	60 (70.6)	71 (79.8)	131 (75.3)
Female	25 (29.4)	18 (20.2)	43 (24.7)
Race, n (%) [a, b]			
American Indian or Alaskan Native	1 (1.2)	0 (0.0)	1 (0.6)
Asian	23 (27.1)	21 (23.6)	44 (25.3)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
White	50 (58.8)	59 (66.3)	109 (62.6)
Other	11 (12.9)	9 (10.1)	20 (11.5)
Ethnicity, n (%) [a]			
Hispanic or Latino	3 (3.5)	2 (2.2)	5 (2.9)
Non-Hispanic or Latino	82 (96.5)	87 (97.8)	169 (97.1)
Age (years) [c]			
Mean (SD)	41.7 (15.51)	42.9 (17.94)	42.3 (16.76)
Median	40.0	39.0	40.0
Min-Max	18-79	19-88	18-88
APACHE II Scores			
Mean (SD)	6.5 (4.00)	5.9 (4.08)	6.2 (4.04)
Median	6.0	5.0	5.0
APACHE II Score Stratum, n (%) [a]			
≤ 10	71 (83.5)	73 (82.0)	144 (82.8)
> 10 and ≤ 25	14 (16.5)	16 (18.0)	30 (17.2)
Body Mass Index (kg/m^2)			
n	82	89	171
Mean (SD)	24.4 (5.18)	25.4 (4.89)	24.9 (5.04)
Median	23.03	24.49	23.92
Min-Max	15.5-43.3	17.7-41.5	15.5-43.3
Bacteremia			
Present	7 (8.2)	6 (6.7)	13 (7.5)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole.

a Percentages are calculated using the number of subjects with non-missing data in the mMITT Population as the denominator.

b Other race is 'Indian'.

c Age is calculated as the integer part of ([Screening visit date - birth date]/365.25).

Table 28. Primary Diagnosis and Surgical Intervention by Treatment Group – mMITT Population, Study NXL104/2002 (cIAI)

Primary Diagnosis/ Surgical Intervention	***Site of Origin***	***CAZ-AVI + MTZ (N = 85)***	***Meropenem (N = 89)***	***Total (N = 174)***
Anatomic Site of Origin of Current Infection[a]	Stomach/Duodenum	23 (27.1)	18 (20.2)	41 (23.6)
	Gall Bladder	4 (4.7)	9 (10.1)	13 (7.5)
	Small Bowel	4 (4.7)	12 (13.5)	16 (9.2)
	Appendix	41 (48.2)	43 (48.3)	84 (48.3)
	Colon	12 (14.1)	5 (5.6)	17 (9.8)
	Parenchymal (liver)	1 (1.2)	1 (1.1)	2 (1.1)
	Parenchymal (spleen)	0	0	0
	Other	0	1 (1.1)	1 (0.6)
Infection Process[a]	Total	85 (100.0)	89 (100.0)	174 (100.0)
	Single Abscess	21 (24.7)	19 (21.3)	40 (23.0)
	Multiple Abscess	2 (2.4)	4 (4.5)	6 (3.4)
	Localized Peritonitis	32 (37.6)	38 (42.7)	70 (40.2)
	Generalized Peritonitis	39 (45.9)	39 (43.8)	78 (44.8)
	Visceral Perforation	37 (43.5)	36 (40.4)	73 (42.0)
	Other	0	0	0
Type of Procedure	Open Laparotomy	76 (89.4)	80 (89.9)	156 (89.7)
	Laparoscopic Procedure	8 (9.4)	9 (10.1)	17 (9.8)
	Percutaneous Drainage	1 (1.2)	0	1 (0.6)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole.

Note: Percentages are calculated using the number of subjects in the mMITT Population.

a. A subject can have the origin of current infection in more than 1 anatomical site and more than 1 infection process recorded.

Approximately half of the subjects in each treatment group (52.9% CAZ-AVI + MTZ); 49.4% meropenem) received < 24 h of protocol-allowed prior antibiotic therapy. Metronidazole (21.2% and 14.6%, respectively) and third-generation cephalosporins (20.0% and 18.0%, respectively) were the most common prior antibiotics.

The majority of subjects (82.8%) had infections caused by pathogens in the *Enterobacteriaceae* family, with *E. coli* being the most common (70% of subjects) (Table 29). The CAZ-AVI MIC_{90} and MIC ranges associated with *E. coli* were 0.25 mg/L and ≤ 0.03 to 2 mg/L, respectively, and the meropenem MIC_{90} and MIC ranges associated with *E. coli* were 0.015 mg/L and ≤ 0.004 to 0.03 mg/L, respectively. *P. aeruginosa* was the most commonly isolated non-fermenting Gram-negative pathogen. Approximately two-thirds of subjects (60.0% CAZ-AVI + MTZ and 65.2% meropenem) had only 1 pathogen isolated from the intra-abdominal infection site. Enterococci and anaerobes were most often isolated concomitantly with Gram-negative aerobes from polymicrobial cIAI. Approximately 8% of subjects were bacteremic at baseline.

Table 29. Subjects with Most Common (>2 Isolates Per Group) Baseline Pathogens at Baseline – mMITT Population, Study NXL104/2002 (cIAI)

Baseline Pathogen [a]	***CAZ-AVI + MTZ (N = 85) n (%)***	***Meropenem (N = 89) n (%)***	***Total (N = 174) n (%)***
Gram-negative Pathogens (Aerobes)	73 (85.9)	78 (87.6)	151 (86.8)
Enterobacteriaceae	70 (82.4)	74 (83.1)	144 (82.8)
Escherichia coli	60(70.6)	62 (69.7)	122 (70.1)
Klebsiella pneumoniae	8 (9.4)	13 (14.6)	21 (12.1)
Enterobacter cloacae	1 (1.2)	5 (5.6)	6 (3.4)
Gram-negative Pathogens (Aerobes) other than *Enterobacteriaceae*	10 (11.8)	10 (11.2)	20 (11.5)
Pseudomonas aeruginosa	6 (7.1)	5 (5.6)	11 (6.3)
Gram-positive Pathogens (Aerobes)	23 (27.1)	18 (20.2)	41 (23.6)
Enterococcus faecalis	5 (5.9)	3 (3.4)	8 (4.6)
Staphylococcus aureus	5 (5.9)	8 (9.0)	13 (7.5)
Enterococcus faecium	4 (4.7)	4 (4.5)	8 (4.6)
Gram-positive and Gram-negative (Anaerobes)	16 (18.8)	12 (13.5)	28 (16.1)
Bacteroides fragilis	7 (8.2)	4 (4.5)	11 (6.3)
Clostridium ramosum	3 (3.5)	1 (1.1)	4 (2.3)
Bacteroides thetaiotaomicron	2 (2.4)	3 (3.4)	5 (2.9)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole.

a Only pathogens isolated in > 1 subject shown.

Baseline pathogens containing any type of β-lactamase resistance mechanism were isolated from 31.6% (55/174) of subjects in the mMITT Population. The most common class of β-lactamase gene was ESBL (25.3%, 44/174), and $bla_{CTX\text{-}M\text{-}15}$ in combination with other genes was the most common β-lactamase gene (20.7%, 36/174). The distribution of β-lactamase genotypes was similar between treatment groups.

A total of 53 subjects were infected with a CAZ-NS pathogen(s), defined as bacterial isolates whose susceptibility results are classified as "intermediate" or "resistant" using CLSI methodology (CLSI, 2013). Specifically, for *Enterobacteriaceae* and *P. aeruginosa*, CAZ-NS was defined as ceftazidime MIC ≥ 8 mg/L and MIC ≥ 16 mg/L, respectively. Efficacy results for subjects infected with a CAZ-NS pathogen are presented in Section 4.5.3.1 for this study and in Section 4.5.3.4 (combined with interim data from the Resistant Pathogen study).

4.5.1.4 Efficacy Results

4.5.1.4.1 Primary Efficacy Analysis

In the mMITT Population, the clinical cure rates were 82.4% for CAZ-AVI + MTZ and 88.8% for meropenem (95% CI for treatment difference: -17.3, 4.2) (Table 30). Of note, 4 out of the 7 failures in the CAZ-AVI group had polymicrobial cIAI that included enterococcal species or anaerobes. In contrast, all 5 of the meropenem failures had monomicrobial cIAI caused by an aerobic Gram-negative pathogen. Over half the treatment difference was due to imbalance in the indeterminate rate, with the most common reason for indeterminate clinical response being missing assessment at TOC (5 CAZ-AVI + MTZ subjects and 3 meropenem subjects). No subjects with clinical failure had microbiological outcomes of persistence with postbaseline acquisition of resistance (≥ 4-fold increase in baseline MIC).

Table 30. Clinical Response at TOC by Treatment Group – Study NXL104/2002 (cIAI)

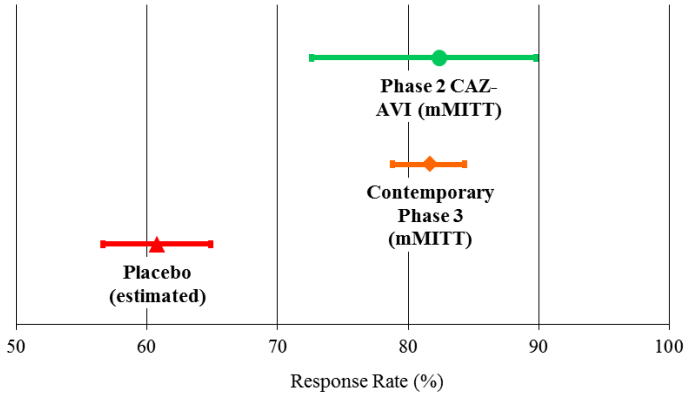
mMITT Population ***Response***	***CAZ-AVI + MTZ*** ***N = 85*** ***n (%)***	***Meropenem*** ***N = 89*** ***n (%)***	***Difference*** ***[95% CI[a]]***
Cure	70 (82.4)	79 (88.8)	-6.4 [-17.3, 4.2]
Failure	7 (8.2)	5 (5.6)	2.6
Indeterminate	8 (9.4)	5 (5.6)	3.8

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole; TOC = test of cure.
a 95% CI for the difference between treatment groups using the Miettinen-Nurminen method.

As this study was not designed for non-inferiority analysis, efficacy in the mMITT Population was compared with results from contemporary Phase 3 cIAI clinical trials and estimated placebo rate, as presented in the FDA Guidance for Industry for cIAI (FDA, 2012). The 82.4% cure rate from Phase 2 was similar to that observed in contemporary studies (81.7%; 95% CI: 78.8, 84.3) (Figure 8). The CIs from both the Phase 2 study and contemporary studies do not overlap and are higher than the estimated placebo rate (FDA, 2012), demonstrating that the Phase 2 results are consistent with an efficacious antibiotic for the treatment of cIAI.

Figure 8. Comparison of Clinical Cure Rates in Phase 2 CAZ-AVI to Contemporary Phase 3 Studies and Placebo – cIAI

Phase 2 CAZ-AVI (mMITT)	82.4% (95% CI: 72.6, 89.8)
Contemporary Phase 3 (mMITT)	81.7% (95% CI: 78.8, 84.3)
Placebo (estimated)	60.8% (95% CI: 56.6, 64.9)



4.5.1.4.2 Secondary Efficacy Analyses

4.5.1.4.2.1 Clinical Response at End of Intravenous Therapy and Late Follow Up in the mMITT Population

In the mMITT Population, clinical cure rates at EOIV and LFU visits were similar between treatment groups (Table 31).

Table 31. Clinical Response at EOIV & LFU– mMITT Population, Study NXL104/2002 (cIAI)

	CAZ-AVI + MTZ N = 85 n (%) 95% CI [a]	***Meropenem N = 89 n (%) 95% CI [a]***	***Difference[b]***
EOIV			
Cure	78 (91.8) 83.8, 96.6	81 (91.0) 83.1, 96.0	0.8
Failure	3 (3.5)	2 (2.2)	1.3
Indeterminate	4 (4.7)	6 (6.7)	-2.0
LFU			
Cure	71 (83.5) 73.9, 90.7	77 (86.5) 77.6, 92.8	-3.0
Failure	7 (8.2)	6 (6.7)	1.5
Indeterminate	7 (8.2)	6 (6.7)	1.5

a 95% CI for the proportions with favorable response determined using the Clopper-Pearson method.
b CAZ-AVI minus meropenem = observed difference.

4.5.1.4.2.2 Clinical Response by Baseline Pathogen in the mMITT Population

Clinical cure rate by pathogen and treatment group is summarized in Table 32, showing similar clinical cure rates between treatment groups by pathogen, and across pathogens within each treatment group for Gram-negative aerobes.

Table 32. Clinical Cure at TOC by Most Common (> 2 Isolates per Group) Baseline Pathogen – mMITT Population, Study NXL104/2002 (cIAI)

Gram Stain Status ***Higher Level Group*** ***Baseline Pathogen[a]***	***CAZ-AVI + MTZ*** ***(N = 85)*** ***n/N1 (%)***	***Meropenem*** ***(N = 89)*** ***n/N1 (%)***
Gram-negative aerobes	59/73 (80.8)	68/78 (87.2)
Enterobacteriaceae	57/70 (81.4)	64/74 (86.5)
Escherichia coli	49/60 (81.7)	55/62 (88.7)
Klebsiella pneumoniae	6/8 (75.0)	11/13 (84.6)
Enterobacter cloacae	1/1 (100.0)	4/5 (80.0)
Gram-negative aerobes other than *Enterobacteriaceae*	9/10 (90.0)	10/10 (100.0)
Pseudomonas aeruginosa	6/6 (100.0)	5/5 (100.0)
Gram-positive aerobes	21/23 (91.3)	18/18 (100.0)
Enterococcus faecalis	5/5 (100.0)	3/3 (100.0)
Staphylococcus aureus	5/5 (100.0)	8/8 (100.0)
Enterococcus faecium	3/4 (75.0)	4/4 (100.0)
Anaerobes	10/16 (62.5)	10/12 (83.3)
Bacteroides fragilis	3/7 (42.9)	3/4 (75.0)
Clostridium ramosum	3/3 (100.0)	1/1 (100.0)
Bacteroides thetaiotaomicron	1/2 (50.0)	2/3 (66.7)

Abbreviations: mMITT = microbiological modified intent-to-treat; MTZ = metronidazole; TOC = Test-of-Cure.

a. Percentages are calculated using the number of subjects with an assessment with a given baseline pathogen (N1) in the mMITT Population as the denominator. A single subject may have had multiple isolates and is counted under each baseline pathogen.

4.5.1.4.3 Subgroup Analyses

Clinical cure at TOC was generally consistent across subgroups defined by baseline characteristics, including APACHE II score; primary site of infection; monomicrobial and polymicrobial infection; age, race, and gender; prior antibiotic use; and bacteremia. Regarding the latter, all 13 subjects in mMITT Population with bacteremia (7 CAZ-AVI and 6 meropenem subjects) were clinical cures at TOC. The subgroup analyses were exploratory in nature and results among these small groups were considered hypothesis-generating.

4.5.2 Phase 2 cUTI Study (NXL104/2001)

4.5.2.1 Study Methodology

Study Design

Study NXL104/2001 was a Phase 2, descriptive, multinational, randomized, investigator-blinded study of hospitalized adult subjects with cUTI. Subjects were stratified based on the type of infection (pyelonephritis or other cUTI without pyelonephritis) and randomized 1:1 to CAZ-AVI or imipenem-cilastatin (hereafter referred to as imipenem).

The study enrolled subjects from the US, India, Lebanon, Guatemala, and Jordan. These countries were selected to enrich for enrollment of subjects with infections caused by CAZ-NS (eg, ESBL-producing) pathogens.

The dosage of CAZ-AVI was 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) administered q8h as a 30-minute IV infusion. This was based on the US labeling for ceftazidime (FORTAZ package insert, 2010) and a 4:1 ratio of CAZ-AVI based on early animal studies of the combination. The dose of CAZ-AVI used in this study (500/125 mg) was 4-fold lower than the proposed labeled dose (2000/500 mg) and was infused over a shorter interval (30 minutes vs. 2 h for the proposed labeled dose). At the time of study initiation, FDA was concerned with using a higher dose of ceftazidime than was approved for this indication; however, based on subsequent extensive PK/PD analyses, the current proposed dose of 2.5 g CAZ-AVI q8h infused over 2 h is required to cover pathogens with CAZ-AVI MICs up to 8 mg/L. In addition, the lower dose does not take into account the importance of adequate drug concentrations at extra-urinary sites for infections due to pathogens with MICs close to the breakpoint. Patients with cUTI may have associated bacteremia, renal parenchymal abscess, and perinephric abscess. Such extra-urinary involvement may not be initially evident, and administration of a dosage adequate to produce sufficient tissue and plasma concentrations would be important (Sobel and Kaye, 2010).

Imipenem (0.5 g IV q6h) was selected as the active comparator based on its established efficacy against Gram-negative pathogens (including ESBL-producing strains) routinely isolated in cUTI, and it is FDA-approved and widely used for cUTI treatment (PRIMAXIN® package insert, 2012).

Subjects received at least 4 days of IV study drug. If, after at least 4 days of IV therapy, subjects met protocol-specified criteria for clinical improvement, they were permitted to switch to oral therapy (open-label ciprofloxacin 500 mg administered q12h) to complete the treatment course unless the subject's baseline pathogen(s) demonstrated resistance to the fluoroquinolone or the subject was intolerant of or had a documented allergy to it. Subjects were to receive a minimum of 7 days and a maximum of 14 days of total antibiotic therapy (IV plus oral therapy).

The study was designed to enroll a subject population that was consistent with the FDA Guidance for Industry for cUTI at the time of study initiation. Key inclusion criteria included age ≥ 18 years to ≤ 90 years and clinically suspected and/or bacteriologically documented acute pyelonephritis or other cUTI judged by the investigator to be serious (requires parenteral therapy) according to protocol-defined clinical diagnostic criteria. As part of these criteria, all subjects were required to have both pyruria (determined by a midstream clean-catch or catheterized urine specimen with ≥ 10 WBCs per high power field) and positive urine culture (≥ 10^5 CFU/mL of a recognized uropathogen presumed or known to be susceptible to the parenteral study antibiotics). The category of "other cUTI" included infection in a male in whom the diagnosis of acute prostatitis is excluded by physical exam; infection in a female with presence of an indwelling catheter, current use of intermittent bladder catheterization, or instrumentation of the urinary tract, including recent urogenital surgery; or functional or anatomical abnormalities of the urinary tract (eg, partial obstructive uropathy, elevated postvoiding residual volume, or neurogenic bladder).

Patients could have been enrolled before urine culture results were available if it was likely the results were (based on urinalysis and clinical findings) to be positive. However, a urine Gram stain must have been performed and have demonstrated the presence of Gram-negative bacilli before study entry if a culture result was not available. Subjects whose admission urine culture contained a uropathogen at a count of < 10^5 CFU/mL should have remained in the study. If the admission urine culture did not contain a recognized uropathogen in any amount, the subject should have been withdrawn from the study.

Key exclusion criteria included: documented uropathogen resistant to one or both study drugs; receipt of ≥ 1 dose of a potentially effective systemic antibiotic after obtaining the urine culture or within 48 h before the urine culture (except in cases of documental prior antibiotic failure); receipt of prophylactic antibiotic therapy (eg, nitrofurantoin) unless the admission culture was known to contain ≥ 10^5 CFU/mL of a recognized uropathogen; complete obstruction of any portion of the urinary tract; perinephric or intrarenal abscess; prostatitis; ileal loops or vesico-ureteral reflux; renal transplant recipients; permanent indwelling catheter or instrumentation including nephrostomy; estimated CrCL < 70 mL/min by Cockcroft-Gault formula; and evidence of abnormal liver function (eg, ALT, AST, bilirubin, or alkaline phosphatase > 3 times ULN).

Determination of Microbiological & Clinical Responses

Urine samples were obtained at study entry, Day 3 to 5 during therapy, EOIV, TOC, LFU, and at other time points as clinically indicated. Microbiological assessments of the specimens included Gram's stain, WBC, and culture. Two sets of blood specimens for culture were obtained at baseline from catheterized subjects and subjects with stents and post-baseline if prior blood cultures were positive.

Microbiological response was determined for each baseline pathogen isolated from urine and/or blood at EOIV, TOC, and LFU. Microbiological eradication was defined as a urine culture showing reduction in baseline uropathogen to $< 10^4$ CFU/mL and pathogen was not present in the blood. Microbial persistence was defined as a urine culture showing $\geq 10^4$ CFU/mL of the baseline uropathogen. A favorable microbiological outcome included responses of eradication and presumptive eradication. If more than 1 causative pathogen was isolated from the pre-treatment culture(s) and the microbiological outcome was not the same for all pathogens, the subject was classified as having an unfavorable outcome if the outcome of at least 1 pathogen fell into this category.

Similarly, clinical assessments were performed at baseline, during IV study antibiotic therapy (Day 3, 4, or 5), at EOIV, at TOC 5 to 9 days after antibiotic (oral and IV) therapy, and at LFU. At each visit during IV therapy, a blinded investigator made an assessment of the subject's overall clinical status to determine appropriate timing of the switch to oral therapy and total duration of therapy.

Clinical cure was defined as all or most pre-therapy signs and symptoms of the index infection had resolved and no additional antibiotic was required. Clinical failure was defined as no apparent response to therapy; persistence or progression of most/all pre-therapy signs and symptoms or use of additional antibiotic therapy for the current infection.

Primary & Secondary Efficacy Outcomes

The primary efficacy outcome is the favorable microbiological response rate at TOC. The protocol-defined primary analysis was determined from the ME Population; however, in consultation with the FDA, the mMITT Population was used for the primary analysis in this submission.

Secondary efficacy outcomes presented in this Briefing Document include: microbiological outcome at EOIV and LFU in the mMITT Population, microbiological outcome by baseline uropathogen, and clinical outcome at EOIV, TOC, and LFU in the mMITT Population.

The mMITT Population included all randomized subjects who received at least 1 dose of study drug and had a study qualifying pre-treatment urine culture containing $> 10^5$ CFU/mL of ≥ 1 uropathogen.

Statistical Analyses

This Phase 2 study was not statistically powered to demonstrate non-inferiority to the comparator. For microbiological (ie, eradication) and clinical response (ie, cure) outcomes, 95% CIs for the proportions of subjects with favorable responses were determined using the Clopper-Pearson method, and the 95% CIs for the differences between treatment groups were determined using the nonstratified Miettinen-Nurminen method (Miettinen and Nurminen, 1985) or the 2-sided test for proportions with continuity correction.

4.5.2.2 Subject Disposition

Overall, 137 subjects were randomized to study drug, 69 to CAZ-AVI and 68 to imipenem; 1 subject in each treatment group did not receive a dose of study drug (Table 33). Most subjects in both treatment groups (72.5% in the CAZ-AVI + MTZ group and 82.4% in the imipenem group) completed a full course of IV study drug. Of those who discontinued IV study drug prematurely, the most common reason for discontinuation was "did not meet inclusion/exclusion criteria"; these subjects were enrolled based on urine Gram stain results revealing Gram-negative bacteria, but subsequent urine cultures did not meet minimum CFU criteria.

Table 33. Subject Disposition – Safety Population, Study NXL104/2001 (cUTI)

	CAZ-AVI n (%)	*Imipenem n (%)*	*Total*
Randomized	69	68	137
Received a Dose of Study Drug	68 (98.6%)	67 (98.5%)	135 (98.5%)
Completed Intended Study Treatment	50 (72.5)	56 (82.4)	106 (77.4)
Discontinued IV Study Drug	19 (27.5)	12 (17.6)	31 (22.6)
Reasons for Discontinuation of IV Study Drug			
Did not meet inclusion/exclusion criteria	13 (18.8)	10 (14.7)	23 (16.8)
Adverse event	0	0	0
SAE	1 (1.4)	0	1 (0.7)
Investigator decision	0	1 (1.5)	1 (0.7)
Protocol deviation	1 (1.4)	1 (1.5)	2 (1.5)
Withdrew consent	2 (2.9)	0	2 (1.5)
Lost to follow up	1 (1.4)	0	1 (0.7)
Other[a]	1 (1.4)	0	1 (0.7)
Completed Study	49 (71.0)	54 (79.4)	103 (75.2)

Abbreviation: SAE = serious adverse event.

Notes: Percentages are calculated using the number of randomized subjects as the denominator.

If study treatment not completed, the same subject might be counted in different categories.

a Subject 20603 had a death in the family and was discharged against medical advice.

A total of 135 subjects were included in the Safety Population and 95 in the mMITT Population (Table 34).

Table 34. Subject Evaluability for Analysis Populations – Study NXL104/2001 (cUTI)

	CAZ-AVI n (%)	***Imipenem n (%)***	***Total n (%)***
Randomized	69 (100%)	68 (100%)	137 (100%)
Safety Population[a]	68 (98.6%)	67 (98.5%)	135 (98.5%)
mMITT Population	46 (66.7%)	49 (72.1%)	95 (69.3%)

Abbreviations: mMITT = microbiological modified intent-to-treat; N = number of subjects in each treatment group (denominator); n = number of subjects in each category.

a. All subjects who received study therapy. Percentages are calculated using the randomized subjects as the denominator.

Subjects were randomized at 26 sites in 5 countries, with enrollment by country balanced between the 2 treatment groups for subjects in the mMITT Population (Table 35).

Table 35. Subjects Entered into Study by Country and Treatment Group- mMITT Population, Study NXL104/2001 (cUTI)

Country	***CAZ-AVI (N = 46) n (%)***	***Imipenem (N = 49) n (%)***	***Total (N = 95) n (%)***
United States	8 (17.4)	6 (12.2)	14 (14.7)
India	3 (6.5)	3 (6.1)	6 (6.3)
Lebanon	15 (32.6)	18 (36.7)	33 (34.7)
Guatemala	10 (21.7)	12 (24.5)	22 (23.2)
Jordan	10 (21.7)	10 (20.4)	20 (21.1)

Abbreviation: mMITT = microbiological Modified Intent-to-Treat.

4.5.2.3 Demographic and Baseline Characteristics

The treatment groups were balanced based on demographic and other baseline characteristics (Table 36). Approximately two-thirds (62%) had acute pyelonephritis (Table 37). Few subjects had indwelling urinary catheters or stents at baseline; all except 1 subject (in the imipenem group) underwent removal of the device within 24 h of the first study drug dose as directed per protocol. These baseline characteristics are similar to those reported among subjects enrolled in recent Phase 3 cUTI studies.

Table 36. Demographic and Baseline Characteristics – mMITT Population, Study NXL104/2001 (cUTI)

	***CAZ-AVI* (N = 46)**	***Imipenem* (N = 49)**	***Total* (N = 95)**
Age (years)[a]			
Mean (SD)	44.5 (16.73)	49.5 (18.69)	47.1 (17.85)
Min, Max	19, 85	18, 89	18, 89
Sex, n (%)			
Male	9 (19.6)	14 (28.6)	23 (24.2)
Female	37 (80.4)	35 (71.4)	72 (75.8)
Ethnicity, n (%)			
Hispanic or Latino	12 (26.1)	12 (24.5)	24 (25.3)
Non-Hispanic or Latino	34 (73.9)	37 (75.5)	71 (74.7)
Race, n (%)			
White or Caucasian	29 (63.0)	32 (65.3)	61 (64.2)
Black or African American	1 (2.2)	4 (8.2)	5 (5.3)
Asian	4 (8.7)	3 (6.1)	7 (7.4)
Other[b]	12 (26.1)	10 (20.4)	22 (23.2)
Baseline bacteremia			
Present	3 (6.5)	3 (6.1)	6 (6.3)

Abbreviations: CFU= colony forming unit; mMITT = microbiological Modified Intent-to-Treat.

a Calculated by subtracting date of birth from date of informed consent and converting to years.

b Other includes Mexican, Mexican American, and Multiracial.

Table 37. Summary of Primary Diagnoses – mMITT Population, Study NXL104/2001 (cUTI)

	***CAZ-AVI* (N = 46) n (%)**	***Imipenem* (N = 49) n (%)**	***Total* (N = 94) n (%)**
Acute pyelonephritis	30 (65.2)	29 (59.2)	59 (62.1)
cUTI without acute pyelonephritis	16 (34.8)	20 (40.8)	36 (37.9)
Urinary tract abnormalities at baseline	15 (32.6)	20 (40.8)	35 (36.8)
Partial obstructive uropathy acquired	5 (10.9)	4 (8.2)	9 (9.5)
Structural abnormality	1 (2.2)	3 (6.1)	4 (4.2)
Elevated post voiding residual volume (≥ 100 mL)	0	4 (8.2)	4 (4.2)
Neurogenic bladder	5 (10.9)	2 (4.1)	7 (7.4)
Other	5 (10.9)	10 (20.4)	15 (15.8)

Abbreviation: mMITT = microbiological modified intent-to-treat.

Note: Subjects can be counted in > 1 category.

Few subjects (15.2% CAZ-AVI and 12.2% imipenem) had received protocol-allowed antibiotic therapy prior to study enrollment.

The majority of subjects (94.7%) had infections caused by pathogens in the *Enterobacteriaceae* family, with *E. coli* being the most common (90% of subjects) (Table 38); 6.1% of subjects were bacteremic at baseline (Table 36). The CAZ-AVI MIC_{90} and range for *E. coli* were 0.25 mg/L and ≤ 0.03 to 0.25 mg/L, respectively, and the imipenem MIC_{90} and range for *E. coli* were 0.12 mg/L and 0.06 to 0.25 mg/L. Only 5 subjects (5.3%) had cUTI due to *P. aeruginosa*.

Table 38. Subjects with Uropathogens Isolated from Urine or Blood Specimens – mMITT Population, Study NXL104/2001 (cUTI)

Gram Stain Status ***Higher Level Group*** ***Baseline Pathogen[a]***	***CAZ-AVI*** ***(N = 46)*** ***n (%)***	***Imipenem*** ***(N = 49)*** ***n (%)***
Number of subjects with a uropathogen	46 (100.0)	49(100.0)
Gram-negative pathogens (aerobes)	46 (100.0)	49(100.0)
Enterobacteriaceae	43 (93.5)	47 (95.9)
Escherichia coli	43 (93.5)	42 (85.7)
Gram-negative pathogens (aerobes) other than *Enterobacteriaceae*	3 (6.5)	2 (4.1)
Pseudomonas aeruginosa	3 (6.5)	2 (4.1)

Abbreviation: mMITT = microbiological modified intent-to-treat.

[a] Selected pathogens displayed if isolated from ≥ 2 subjects.

Baseline pathogens containing any type of β-lactamase resistance mechanism were isolated from almost half (44/95) of subjects in the mMITT Population. Approximately 30% of subjects in both treatment groups were infected at baseline with *E. coli* possessing $bla_{CTX\text{-}M\text{-}15}$, a member of CTX-M-type β-lactamases that exhibit ESBL properties. Other identified β-lactamase encoding genes included TEM-, SHV-, and CTX-M-type ($bla_{CTX\text{-}M\text{-}14}$, $bla_{TEM\text{-}1}$, and $bla_{SHV\text{-}12}$ [Class A]); OXA-type ($bla_{OXA\text{-}30}$ [Class D]) and plasmid-mediated ($bla_{CMY\text{-}2}$ [Class C]) genes.

A total of 32 subjects (33.7%) were infected with a CAZ-NS pathogen(s) at baseline. Efficacy results for subjects infected with a CAZ-NS pathogen are presented in Section 4.5.3.2 for this study and in Section 4.5.3.4 (combined with interim data from the Resistant Pathogen study).

4.5.2.4 Efficacy Results

4.5.2.4.1 Primary Efficacy Analysis

Approximately two-thirds of subjects in the mMITT Population (67.4% CAZ-AVI, 63.3% imipenem) had a favorable microbiological outcome at TOC (95% CI for treatment difference -15.1, 22.9) (Table 39). None of the cases with persistence were associated with a pathogen showing development of resistance (defined as > 4-fold increase in MIC).

Table 39. Summary of Microbiological Outcome at TOC – mMITT Population, Study NXL104/2001 (cUTI)

mMITT Population Outcome	***CAZ-AVI N = 46 n (%)***	***Imipenem N = 49 n (%)***	***Difference 95% CI[b]***
Favorable *95% CI[a]*	31 (67.4) 52.0, 80.5	31 (63.3) 48.3, 76.6	4.1 -15.1, 22.9
Unfavorable[c]	10 (21.7)	14 (28.6)	-6.8
Indeterminate[d]	5 (10.9)	4 (8.2)	2.7

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

a 95% CI for the difference between treatment groups using the non-stratified Miettinen-Nurminen method.

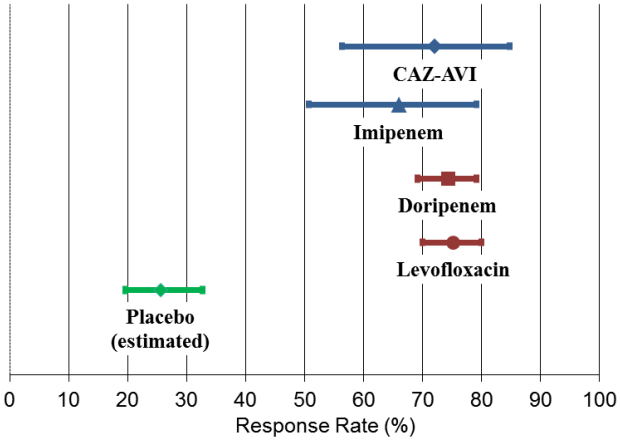
As this study was not designed for non-inferiority analysis, the outcome in the mMITT Population was compared with results from contemporary Phase 3 cUTI clinical trials and estimated placebo rate, as presented in the FDA Guidance for Industry for cUTI (FDA, 2012). The 67.4% favorable microbiological response rate associated with CAZ-AVI in this Phase 2 study was lower than that observed for other systemic antibacterial agents in contemporary Phases 3 studies (79.6%; 95% CI: 77.2, 81.8); however, the 95% CIs overlap. Given the small sample size in this Phase 2 study, the overall microbiologic and clinical response rates should be interpreted within the context of the totality of the data, as the Phase 2 study was designed for descriptive statistics. While the microbiological eradication rates in the Phase 2 study may appear lower than expected, comparative analyses presented below demonstrate that the microbiological and clinical response rates are consistent with expectations for that of an efficacious drug.

In addition, this Phase 2 cUTI study used a dosage of CAZ-AVI of 625 mg (25% of the proposed marketed dosage); however, PTA analyses showed that in order to achieve > 90% PTA for organisms up to an MIC of 8 mg/L, a dose of 2.5 g CAZ-AVI is required. For example, as described in Section 4.5.2.4.2.3 below, there was no eradication of baseline *Pseudomonas* in 5 subjects (3 CAZ-AVI and 2 imipenem). These pathogens had CAZ-AVI MICs many fold higher than those associated with the *Enterobacteriaceae* group and were unlikely to be susceptible to the dose of CAZ-AVI used in the Phase 2 study based on PTA analyses. Therefore, it is more appropriate to compare the microbiological outcomes for *Enterobacteriaceae* from Phase 2 compared with a similar population from the comparative Phase 3 studies. Unfortunately, comparative data for the *Enterobacteriaceae* subgroup in the mMITT Population are unavailable in most publications on cUTI; however, as presented in Figure 9 the microbiological eradication rates noted for the *Enterobacteriaceae* subset in both treatment arms in the Phase 2 CAZ-AVI study are consistent with the mMITT response rates for *Enterobacteriaceae* seen in the Phase 3 trial of doripenem vs. levofloxacin (DORI-05; Kaniga et al, 2010).

Of note, both the CIs from the Phase 2 study and contemporary studies do not overlap and are higher than the estimated placebo rate (FDA, 2012) (Figure 9), demonstrating that the Phase 2 results are consistent with an efficacious antibiotic for the treatment of cIAI.

Figure 9. Favorable Microbiological Outcome Rates in *Enterobacteriaceae* - Phase 2 CAZ-AVI and Phase 3 Doripenem Studies - mMITT Population, cUTI

Phase 2 cUTI (NXL104/2001)	
CAZ-AVI	72.1% (95% CI: 56.3, 84.7)
Imipenem	66.0% (95% CI: 50.7, 79.1)
Phase 3 cUTI (DORI-05; Kaniga et al, 2010)	
Doripenem	74.3% (95% CI: 69.1, 79.2)
Levofloxacin	75.2% (95% CI: 70.0, 80.0)
Historical Placebo (FDA, Feb 2012)	
Placebo (estimated)	25.6% (95% CI: 19.6, 32.7)



4.5.2.4.2 Secondary Efficacy Analyses

4.5.2.4.2.1 Clinical Response at TOC in the mMITT Population

Rates of favorable clinical outcomes at TOC were 80.4% in the CAZ-AVI group and 73.5% in the imipenem group (Table 40).

Table 40. Summary of Clinical Outcome at TOC – Study NXL104/2001

mMITT Population Outcome	***CAZ-AVI N = 46 n (%)***	***Imipenem N = 49 n (%)***	***Difference 95% CI[b]***
Cure *95% CI[a]*	37 (80.4) 66.1, 90.6	36 (73.5) 58.9, 85.1	7.0 -10.4, 23.9
Failure[c]	5 (10.9)	9 (18.4)	-7.5
Indeterminate[c]	4 (8.7)	4 (8.2)	0.5

Abbreviations: mMITT = microbiological Modified Intent-to-Treat.

a 95% CI for the proportions with favorable response determined using the Clopper-Pearson method.

b 95% CI for the difference between treatment groups using the nonstratified Miettinen-Nurminen method.

c Failure = No apparent response to therapy; persistence or progression of most/all pre-therapy signs and symptoms or use of additional antibiotic therapy for the current infection. Indeterminate = Subjects lost to follow-up such that a determination of clinical response could not be made.

4.5.2.4.2.2 Microbiological Outcome at EOIV and LFU in the mMITT Population

Favorable microbiological outcome rates were 87% in the CAZ-AVI group and 91.8% in the imipenem group at EOIV, and 50% and 46.9%, respectively, at LFU (Table 41). The favorable microbiological outcome rates decreased over the course of the study because outcomes of microbiological persistence were carried forward at each subsequent visit (from EOT to TOC to LFU), indeterminate responses were included in the denominator at each visit, and microbiological recurrences over time are not uncommon in cUTI. This phenomenon of decreased favorable microbiological outcome rates between EOIV and TOC has been observed in recent Phase 3 cUTI trials, including ertapenem versus ceftazidime (Wells, 2004) and doripenem versus levofloxacin (Redman, 2010).

Table 41. Summary of Microbiological Outcome at EOIV and LFU – mMITT Population, Study NXL104/2001 (cUTI)

	CAZ-AVI (N = 46) n (%)	***Imipenem (N = 49) n (%)***	***Observed Difference 95% CI[a]***
EOIV[b]			
Eradication	40 (87.0)	45 (91.8)	-4.9 (-18.8, 8.3)[a]
Persistence	1 (2.2)	0	
Indeterminate	5 (10.9)	4 (8.2)	
LFU[b]			
Sustained eradication	23 (50.0)	23 (46.9)	3.1 (-16.9, 22.8)
Persistence	10 (21.7)	14 (28.6)	
Recurrence	7 (15.2)	3 (6.1)	
Indeterminate	6 (13.0)	9 (18.4)	

Abbreviations: EOIV = End of Intravenous Therapy visit; LFU = Late Follow-up; mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

a. CIs are for differences in proportions (CAZ-AVI overall eradication rate minus imipenem overall eradication rate).

b. Percentages are based on total at each visit.

4.5.2.4.2.3 Microbiological Outcome by Baseline Uropathogen in the mMITT Population

At TOC, eradication of *E. coli*, the predominant uropathogen isolated, occurred in numerically higher proportion of subjects treated with CAZ-AVI compared to imipenem (Table 42). Persistence occurred in all 5 subjects (3 CAZ-AVI and 2 imipenem) infected with *P. aeruginosa*. Of note, the dose of CAZ-AVI used in this study (500/125 mg) is lower than the proposed labeled dose (2000/500 mg) and was infused over a shorter interval (30 minutes vs. 2 h for the proposed labeled dose) and the imipenem dose used in this study (500 mg q6h) was lower than that recommended for moderate to severe infections due to *Pseudomona*s (ie, 1000 mg q8h or q6h, PRIMAXIN package insert, 2012). In contrast, all cIAI subjects infected with *P. aeruginosa* and treated with CAZ-AVI at the proposed dose were clinically cured and had a favorable microbiological response (Section 4.5.1.4.2.2).

Table 42. By-Pathogen Favorable Microbiological Outcome at TOC for Uropathogens (Urine and Blood, All Isolates) – mMITT Population, Study NXL104/2001 (cUTI)

Gram Stain Status ***Higher Level Group*** ***Baseline Pathogen[a]***	***CAZ-AVI*** ***(N = 46)*** ***n/N1 (%)***	***Imipenem*** ***(N = 49)*** ***n/N1 (%)***
Gram-negative pathogens (aerobes)	31/46 (67.4)	31/49 (63.3)
Enterobacteriaceae	31/43 (72.1)	31/47 (66.0)
Escherichia coli	31/43 (72.1)	26/42 (61.9)
Gram-negative pathogens (aerobes) other than *Enterobacteriaceae*	0/3 (0.0)	0/2 (0.0)
Pseudomonas aeruginosa	0/3 (0.0)	0/2 (0.0)

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.

a Baseline uropathogens and blood isolates that are also baseline uropathogens are included.

4.5.2.4.2.4 Clinical Outcome at EOIV and LFU in the mMITT Population

Clinical cure rates in the mMITT Population at both EOIV and LFU were similar for both treatment groups. As expected for cUTI studies where relapses are common, the favorable response rates decrease with later outcome assessments (Table 43).

Table 43. Summary of Clinical Outcome at EOIV and LFU – mMITT Population, Study NXL104/2001 (cUTI)

	CAZ-AVI (N = 46) n (%)	*Imipenem (N = 49) n (%)*	*Difference (95% CI[a])*
EOIV[b]			
Clinical cure	43 (93.5)	46 (93.9)	-0.4 (-12.3, 11.1)
Clinical failure	0	2 (4.1)	
Indeterminate	3 (6.5)	1 (2.0)	
LFU[b]			
Sustained clinical cure	33 (71.7)	32 (65.3)	6.4 (-12.4, 24.7)
Clinical failure (carried forward from TOC)	5 (10.9)	9 (18.4)	
Clinical relapse	3 (6.5)	6 (12.2)	
Indeterminate	5 (10.9)	2 (4.1)	

a 95% CI for the difference between treatment groups using the nonstratified Miettinen-Nurminen method.
b Percentages are based on total at each visit.

4.5.2.4.3 Subgroup Analyses

Microbiological success at TOC was generally consistent across subgroups defined by baseline characteristics, including primary diagnosis; age, race, and gender; and bacteremia. Regarding the latter, 5/7 (71.4%) CAZ-AVI subjects and 4/6 (66.7%) imipenem subjects in mMITT Population with bacteremia had a favorable microbiological response at TOC. The subgroup analyses were exploratory in nature and results among these small groups were considered hypothesis-generating.

4.5.3 Efficacy in cIAI and cUTI Caused by CAZ-NS Pathogens

Subjects with CAZ-NS pathogens represent a key subgroup and analyses of the response rates for these subjects is of particular importance to demonstrate the efficacy of CAZ-AVI in the treatment of cIAI and cUTI caused by MDR Gram-negative pathogens and for infections with limited treatment options. For the purpose of these analyses, CAZ-NS was defined as bacterial isolates whose susceptibility results were classified as "intermediate" or "resistant" using CLSI methodology (CLSI, 2013). Specifically, for *Enterobacteriaceae* and *P. aeruginosa*, CAZ-NS was defined as ceftazidime MIC $\geq$ 8 mg/L and MIC $\geq$ 16 mg/L, respectively.

These analyses include data from an ongoing Resistant Pathogen study, which will be described below in Section 4.5.3.3; as of the interim cutoff date for the NDA (09 Dec 2013), there were 48 subjects infected by CAZ-NS pathogens (44 with cUTI and 4 with cIAI). In the Phase 2 mMITT Populations, there were 85 subjects infected with a CAZ-NS pathogen (53 in Phase 2 cIAI and 32 in Phase 2 cUTI).

Microbiological and clinical outcomes for the subset of subjects infected with a CAZ-NS pathogen is presented in Section 4.5.3.1 for the Phase 2 cIAI study and in Section 4.5.3.2 for the Phase 2 cUTI study. In Section 4.5.3.4, the results for these subsets of subjects are pooled with the respective outcomes from the ongoing Resistant Pathogen study.

The pooled analysis of all subjects with CAZ-NS pathogens is presented in accordance with the *Draft Guidance for Industry, Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (FDA, 2013) which, in the context of a "prospective active-controlled clinical trial in patients with serious bacterial disease and unmet medical need", states that "such a trial can be conducted in a patient population enriched for an unmet need... The trial...(also) could enroll patients with bacterial disease at any one of several different body sites." The Sponsor acknowledges that the pooling of subjects with CAZ-NS pathogens within each indication and across both indications was not prospectively planned and that limitations of interpreting this data exist (discussed further in 4.5.3.4.1).

4.5.3.1 Phase 2 cIAI Caused by CAZ-NS Pathogens (NXL104/2002)

In the Phase 2 cIAI study, 53 subjects (30 subjects in CAZ-AVI group; 23 subjects in meropenem group) were infected with a CAZ-NS pathogen at baseline. Clinical cure rates at TOC were similar between the two treatment groups (Table 44).

Table 44. Clinical Cure at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Study NXL104/2002 (cIAI)

Pathogen Subgroup	*CAZ-AVI + MTZ* *N = 85* *n (%)* *90% CI[a]*	*Meropenem* *N = 89* *n (%)* *90% CI[a]*	*Difference* *90% CI[b]*
CAZ-NS	27/30 (90.0) 76.1, 97.2	19/23 (82.6) 64.5, 93.8	7.4 -8.5, 25.3

Abbreviations: CAZ-I= ceftazidime; CAZ-NS = ceftazidime non-susceptible; CAZ-R = ceftazidime resistant; CAZ-S = ceftazidime susceptible; Meropenem-S = meropenem susceptible; MTZ = metronidazole

Notes: Includes all pathogens (site of infection and blood) using highest MIC isolate. N1 = Number of subjects with a pathogen in the specified category.

a 90% CI for the proportions with favorable response determined using the Clopper-Pearson method.

b 90% CI for the difference between treatment groups using the non-stratified Miettinen-Nurminen method.

4.5.3.2 Phase 2 cUTI Caused by CAZ-NS Uropathogens (NXL104/2001)

In the Phase 2 cUTI study, 32 subjects (14 subjects in CAZ-AVI group; 18 subjects in imipenem group) were infected with a CAZ-NS pathogen at baseline. Microbiological eradication rates at TOC were 64.3% in the CAZ-AVI group and 55.6% in the imipenem group (Table 45).

Table 45. Favorable Microbiological Outcome at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Study NXL104/2001 (cUTI)

Pathogen Subgroup[a]	*CAZ-AVI (N = 46) n/N (%) 90% CI*[a]	*Imipenem (N = 49) n/N (%) 90% CI*[a]	*Difference 90% CI*[b]
CAZ-NS	9/14 (64.3) 39.0, 84.7	10/18 (55.6) 34.1, 75.6	8.7 -20.2, 35.7

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; n = number of pathogens with favorable assessment per MIC value; N = number of subjects in the mMITT Population; NS = nonsusceptible; TOC = Test-of-Cure.

a 90% CI for the proportions with favorable response determined using the Clopper-Pearson method.

b 90% CI for the difference between treatment groups using the nonstratified Miettinen-Nurminen method.

4.5.3.3 Phase 3 cIAI & cUTI Caused by CAZ-NS Pathogens (Interim Data from Ongoing Resistant Pathogen Study D4280C00006)

The Resistant Pathogen study, D4280C00006, is an ongoing, Phase 3 multinational, multicenter, randomized, open-label study in hospitalized adult subjects with cIAI or cUTI caused by CAZ-NS Gram-negative pathogens. Subjects are stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to CAZ-AVI or BAT, with study drug administered for 5 to 21 days.

This study utilizes the proposed labeled dosage regimen for CAZ-AVI: 2.5 g (2 g ceftazidime + 0.5 g avibactam) q8h as a 2-h IV infusion. The infusion time was prolonged in this study compared to the Phase 2 study (NXL104/2002) based on PK/PD target attainment simulations that found that while a 2 g ceftazidime + 0.5 g avibactam dose is optimal, the 30-minute infusion may not achieve adequate probability of joint PK/PD target attainment for organisms with higher CAZ-AVI MICs. The simulations demonstrated that this would be better achieved by a 2-h infusion (joint PK/PD target attainment ≥ 0.9) (Section 4.4).

The BAT was chosen as the active open-label comparator given the requirement for subjects to have an infection caused by a Gram-negative organism resistant to ceftazidime; many of the isolates are expected to have variable resistance mechanisms including those not mediated by β-lactamases. Thus, the selection of a single antibiotic and dose as appropriate control for all subjects is not possible. Subjects randomized to receive investigator-determined BAT receive doses based on the investigator's standard of care, local susceptibility patterns, and the local label recommendation. The Sponsor-recommended BAT options for cIAI in this study are meropenem, imipenem, doripenem, tigecycline, and colistin; however, investigators are not limited to these options.

Key inclusion criteria for subjects with cIAI include: age 18 to 90 years; CAZ-NS pathogen isolated from an abdominal source during surgical intervention; cIAI meeting specific criteria (eg, diagnosis of cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall, diverticulitis with perforation or abscess, appendiceal perforation or periappendiceal abscess, gastrointestinal perforations, intra-abdominal abscesses, and secondary or tertiary peritonitis); evidence of systemic inflammatory response; and physical exam findings consistent with cIAI. If the subject received appropriate prior empiric antibacterial therapy for a CAZ-NS pathogen, they must either have worsening of objective symptoms or signs of infection after ≥ 48 h of appropriate therapy or lack of improvement of objective symptoms or signs of infection after ≥ 72 h of appropriate therapy. Key exclusion criteria included APACHE II score > 30; infections limited to the hollow viscus; prior liver, pancreas, or small-bowel transplant; or response to 5 to 21 days of antibiotic therapy is considered unlikely.

Key inclusion criteria for subjects with cUTI include: age ≥ 18 years to ≤ 90 years and clinically suspected and/or bacteriologically documented acute pyelonephritis or other cUTI. As part of these criteria, all subjects were required to have both pyruria (determined by a midstream clean-catch or catheterized urine specimen with ≥ 10 WBCs per high power field) and positive urine culture (≥ 10^5 CFU/mL of a recognized uropathogen known to be CAZ-NS). Patients with "other cUTI" must meet qualifying symptom criteria and have documented urinary retention, obstructive uropathy, functional or anatomical abnormality of the urogenital tract (eg, anatomic malformations or neurogenic bladder, or postvoid residual urine volume of ≥ 100 mL), use of intermittent bladder catheterization or presence of an indwelling bladder catheter for ≥ 48 h prior to obtainment of study-qualifying culture, or urogenital procedure (such as cystoscopy or urogenital surgery) ≤ 7 days before study entry prior to obtainment of study-qualifying-culture. Key exclusion criteria include: estimated CrCL < 6 mL/min by Cockcroft-Gault formula or receiving dialysis; evidence of abnormal liver function (eg, ALT, AST, bilirubin, or alkaline phosphatase > 3 times ULN); or response to 5 to 21 days of antibiotic therapy is considered unlikely.

Efficacy is assessed at EOT (within 24 h after completion of the last infusion of study drug), TOC (7 to 10 days after last dose of study drug), and follow-up (28-35 days from randomization).

As of the interim data cutoff for the NDA (09 Dec 2013), 48 subjects were randomized at sites in 7 countries outside of the US; these sites were selected for reasons that included high incidences of cIAI and cUTI caused by CAZ-NS pathogens.

Efficacy results are not shown separately for these interim Phase 3 data; rather, they are presented in Section 4.5.3.4 below in pooled analyses with the CAZ-NS infections from the Phase 2 studies.

4.5.3.4 Pooled cIAI and cUTI Caused by CAZ-NS Pathogens

The results of subjects infected with CAZ-NS pathogens in the Phase 2 studies (NXL104/2001 and NXL104/2002) were pooled with the results of subjects enrolled in the Phase 3 Resistant Pathogen study (D4280C00006) as of an interim cutoff date in order to document the total efficacy experience of CAZ-AVI in cIAI and cUTI caused by CAZ-NS pathogens.

4.5.3.4.1 Statistical Methods

Efficacy analyses included microbiological and clinical response at TOC, microbiological and clinical response by pathogen at TOC, and clinical response at EOIV and LFU in the mMITT Population. For analysis of the pooled studies, the 2-sided 95% CI was computed using the method proposed for stratified designs (stratified by study and indication for the pooling across indications) by Miettinen and Nurminen (Miettinen and Nurminen, 1985). Cochran Mantel-Haenszel weights were used for the stratum weights in the calculation for the CIs.

The mMITT Population includes all randomized subjects who have a diagnosis of cIAI or cUTI caused by a CAZ-NS Gram-negative pathogen and who received ≥ 1 dose of study therapy.

Data are presented for 3 combined subject groups:

- Subjects with cUTI caused by CAZ-NS uropathogens from Study NXL104/2001 and Study D4280C00006 (pooled CAZ-NS cUTI subjects)
- Subjects with cIAI caused by CAZ-NS pathogens from Study NXL104/2002 and Study D4280C00006 (pooled CAZ-NS cIAI subjects)
- All subjects with cUTI or cIAI caused by CAZ-NS pathogens from all three studies (pooled CAZ-NS combined indications)

The analysis population of subjects infected with a CAZ-NS pathogen includes 85 subjects enrolled in Phase 2 studies (53 cIAI subjects and 32 cUTI subjects) and 48 subjects enrolled in the Resistant Pathogen study (44 with cUTI and 4 with cIAI).

All subjects in the comparator group received at least one carbapenem (eg, imipenem, meropenem), either as monotherapy or in combination with colistin or ciprofloxacin.

Limitations exist in the interpretation of data from the pooled studies. The CAZ-AVI dosage was different between studies (eg, the dosage is 4 times higher with a 4-fold longer infusion time in the Phase 3 Resistant Pathogen study compared with the Phase 2 cUTI study); therefore, it is difficult to compare microbiological outcome by pathogen, especially among pathogens with high CAZ-AVI MICs. Another limitation to pooling the data is that study conduct was different between the Phase 2 and Phase 3 studies; the Phase 3 Resistant Pathogen is open-label (but a blinded observer evaluated all clinical outcomes), while the Phase 2 cIAI and cUTI studies were double-blinded and investigator-blinded, respectively.

4.5.3.4.2 Demographics and Baseline Characteristics

The treatment groups were balanced within each of the pooled studies groups based on demographic characteristics (Table 46).

Table 46. Demographic and Baseline Characteristics in Subjects Infected with CAZ-NS Pathogens – mMITT Population

	Pooled cIAI Studies		***Pooled cUTI Studies***	
	CAZ-AVI (N = 31) n (%)	***Comparator (N = 26) n (%)***	***CAZ-AVI (N = 35) n (%)***	***Comparator (N = 41) n (%)***
Age (years)				
Mean	36.5	39.7	54.8	55.5
SD	13.29	16.41	18.03	17.20
Median	35.0	34.5	57.0	57.0
Sex				
Male	24 (77.4)	20 (76.9)	18 (51.4)	24 (58.5)
Female	7 (22.6)	6 (23.1)	17 (48.6)	17 (41.5)
Race				
Asian	18 (58.1)	14 (53.8)	4 (11.4)	3 (7.3)
White	8 (25.8)	8 (30.8)	29 (82.9)	34 (82.9)
Other	5 (16.1)	4 (15.4)	2 (5.7)	4 (9.8)
Ethnicity				
Hispanic or Latino	0 (0.0)	0 (0.0)	1 (2.9)	5 (12.2)
Non-Hispanic or Latino	31 (100.0)	26 (100.0)	34 (97.1)	36 (87.8)
Body Mass Index (kg/m^2)				
n	30	26	35	41
Mean	22.4	22.8	27.8	28.8
SD	3.25	2.61	5.57	6.60
Median	22.5	22.4	26.0	27.7
Min, Max	16, 31	18, 32	18, 47	21, 58

4.5.3.4.3 Efficacy Findings

4.5.3.4.3.1 Microbiological Response at TOC – mMITT Population

Favorable microbiological response rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator agent in each of the CAZ-NS groups pooled by indication, although the 95% CI for difference between treatment groups included 0 in both comparisons (Table 47).

Table 47. Microbiological Response at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population

	Pooled cIAI Studies		***Pooled cUTI Studies***	
Response	***CAZ-AVI (N = 31) n (%)***	***Comparator (N = 26) n (%)***	***CAZ-AVI (N = 35) n (%)***	***Comparator (N = 41) n (%)***
Favorable	28 (90.3)	20 (76.9)	24 (68.6)	21 (51.2)
Difference (95% CI)	13.4 (-8.6, 32.3)		17.4 (-5.1, 38.0)	
Unfavorable	2 (6.5)	2 (7.7)	8 (22.9)	18 (43.9)
Indeterminate	1 (3.2)	4 (15.4)	3 (8.6)	2 (4.9)

Abbreviation: T OC = Test-of-Cure.

4.5.3.4.3.2 Microbiological Response at TOC by Baseline Pathogen – mMITT Population

In the pooled cIAI studies and the pooled cUTI studies, the by-pathogen microbiological response rate at TOC was the same or numerically higher with CAZ-AVI versus the comparator for almost all pathogens isolated (Table 48).

To date, a single subject enrolled in the CAZ-AVI program was infected with a proven KPC carbapenemase-producing pathogen. This subject was enrolled in the Phase 3 Resistant Pathogen study in Romania, had a cUTI caused by a KPC-producing strain of *K. pneumoniae* (baseline CAZ-AVI MIC = 1 mg/L; ceftazidime MIC > 64 mg/L; meropenem MIC > 8 mg/L), and was randomized to CAZ-AVI. The subject had microbiological eradication at both TOC and LFU after therapy with CAZ-AVI.

Table 48. Favorable Microbiological Response at TOC by Most Common (>2 Isolates Per Group) CAZ-NS Baseline Pathogen – mMITT Population

Gram Stain Status Higher Level Group Baseline Pathogen	*Pooled cIAI Studies*		*Pooled cUTI Studies*	
	CAZ-AVI (N = 31) n (%)	*Comparator (N = 26) n (%)*	*CAZ-AVI (N = 35) n (%)*	*Comparator (N = 41) n (%)*
Gram-negative	28/31 (90.3)	20/26 (76.9)	24/35 (68.6)	20/41 (48.8)
Enterobacteriaceae	26/29 (89.7)	19/25 (76.0)	23/34 (67.6)	20/40 (50.0)
E. coli	21/23 (91.3)	15/19 (78.9)	12/18 (66.7)	13/23 (56.5)
K. pneumoniae	3/4 (75.0)	4/6 (66.7)	8/10 (80.0)	5/14 (35.7)

Abbreviation: TOC = Test-of-Cure.

4.5.3.4.3.3 Clinical Response at TOC – mMITT Population

The favorable clinical responses were similar to the favorable microbiological responses (Table 49).

Table 49. Clinical Response at TOC in Subjects Infected with CAZ-NS Baseline Pathogens – mMITT Population

Response	*Pooled cIAI Studies*		*Pooled cUTI Studies*	
	CAZ-AVI (N = 31) n (%)	*Comparator (N = 26) n (%)*	*CAZ-AVI (N = 35) n (%)*	*Comparator (N = 41) n (%)*
Clinical Cure	28 (90.3)	20 (76.9)	30 (85.7)	28 (68.3)
Difference (95% CI)	13.4 (-8.6, 32.2)		17.4 (-2.4, 35.0)	
Clinical Failure	2 (6.5)	2 (7.7)	3 (8.6)	6 (14.6)
Indeterminate	1 (3.2)	4 (15.4)	2 (5.7)	7 (17.1)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

4.5.3.4.3.4 Clinical Response at EOIV and LFU – mMITT Population

Sustained clinical cure rate among subjects infected with a CAZ-NS pathogen was numerically higher for those treated for cIAI than for those treated for a cUTI in both treatment groups, and numerically higher for CAZ-AVI versus comparator in both pooled groups (Table 50).

Table 50. Clinical Response at EOIV and LFU in Subjects with CAZ-NS Baseline Pathogens – mMITT Population

Visit *Response*	*Pooled cIAI Studies*		*Pooled cUTI Studies*	
	CAZ-AVI (N = 31) n (%)	*Comparator (N = 26) n (%)*	*CAZ-AVI (N = 35) n (%)*	*Comparator (N = 41) n (%)*
EOIV				
Clinical Cure	28 (90.3)	21 (80.8)	33 (94.3)	39 (95.1)
Clinical Failure	2 (6.5)	1 (3.8)	0 (0.0)	0 (0.0)
Indeterminate	1 (3.2)	4 (15.4)	2 (5.7)	2 (4.9)
LFU				
Sustained Clinical Cure	28 (90.3)	19 (73.1)	26 (74.3)	24 (58.5)
Clinical Failure (carried Forward from TOC)	2 (6.5)	2 (7.7)	5 (14.3)	11 (26.8)
Clinical Relapse	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.4)
Indeterminate	1 (3.2)	5 (19.2)	3 (8.6)	5 (12.2)

Abbreviations: EOIV = End of IV Therapy; LFU = Late Follow-up; TOC = Test-of-Cure.

4.5.3.4.3.5 Efficacy in All Subjects with CAZ-NS Pathogens Pooled – mMITT Population

The favorable microbiological response rates at TOC for subjects with CAZ-NS pathogens in the mMITT Population for the pooled cIAI and cUTI indications are presented in Table 51. The favorable microbiological response rate at TOC was numerically higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cIAI and cUTI indications, with the lower bound of the 95% CI for the difference between treatment groups being -0.5%.

Table 51. Microbiological Response Rates at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Pooled Indications (cIAI and cUTI)

Response	*Pooled Indications (cIAI and cUTI)*	
	CAZ-AVI (N = 66) n (%)	*Comparator (N = 67) n (%)*
Favorable	52 (78.8)	41 (61.2)
Difference (95% CI)	17.6 (-0.5, 29.9)	
Unfavorable	10 (15.2)	20 (29.9)
Indeterminate	4 (6.1)	6 (9.0)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

The clinical response rates at TOC for subjects with CAZ-NS pathogens in the mMITT Population for the pooled cIAI and cUTI indications are presented in Table 52. The clinical cure rate at TOC was higher for subjects treated with CAZ-AVI compared with a comparator (a carbapenem) in the pooled cIAI and cUTI indications, with the lower bound of the 95% CI for the difference between treatment groups being +1.3%.

Table 52. Clinical Response Rates at TOC in Subjects Infected with CAZ-NS Pathogens – mMITT Population, Pooled Indications (cIAI and cUTI)

	Pooled Studies (cIAI and cUTI)	
Response	***CAZ-AVI (N = 66) n (%)***	***Comparator (N = 67) n (%)***
Clinical Cure	58 (87.9)	48 (71.6)
Difference (95% CI)	16.3 (1.3, 28.7)	
Clinical Failure	5 (7.6)	8 (11.9)
Indeterminate	3 (4.5)	11 (16.4)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

Favorable microbiological response rates at TOC for subjects with CAZ-NS pathogens for the pooled cIAI and cUTI indications are presented in Table 53. Eradication rates for subjects with Gram-negative aerobes including the *Enterobacteriaceae* group, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were numerically higher or similar to those in the comparator group. Of note, all cIAI subjects infected with *P. aeruginosa* and treated with CAZ-AVI at the proposed dose were clinically cured and had a favorable microbiological response.

Table 53. By-Pathogen Favorable Microbiological Response at TOC for CAZ-NS Pathogens – mMITT Population, (Pooled cIAI and cUTI Indications)

Gram Stain Status Higher Level Group Baseline Pathogen[a]	***CAZ-AVI (N = 66) n/N1 (%)***	***Comparator (N = 67) n/N1 (%)***
Gram-negative pathogens (aerobes)	52/66 (78.8)	40/67 (59.7)
Enterobacteriaceae	49/63 (77.8)	39/65 (60.0)
Escherichia coli	33/41 (80.5)	28/42 (66.7)
K. pneumoniae	11/14 (78.6)	9/20 (45.0)
Gram-negative pathogens (aerobes) other than *Enterobacteriaceae*	3/3 (100.0)	2/3 (66.7)
Pseudomonas aeruginosa	2/2 (100.0)	1/2 (50.0)

Abbreviations: CAZ-NS = ceftazidime-nonsusceptible; TOC = Test-of-Cure.

a Baseline uropathogens and blood isolates that are also baseline uropathogens are included.

The pooled analyses presented above further support that avibactam is effective in extending the activity of ceftazidime against CAZ-NS pathogens causing cIAI or cUTI. In combination with PK/PD modeling and PTA analyses, these data also provide support for the use in infections with limited treatment options in other body sites (where CAZ-AVI penetration and PTA has been established) such as HABP/VABP and bacteremia.

5.0 CAZ-AVI SAFETY

Ceftazidime is a marketed antibiotic with a well-established nonclinical and clinical safety profile. Clinical Pharmacology studies demonstrate that there is no DDI between ceftazidime and avibactam (Section 4.3.1). In addition, as summarized in Section 5.1, comprehensive nonclinical toxicology studies indicate that avibactam does not significantly alter the safety profile of ceftazidime.

The clinical safety database for CAZ-AVI includes data from 21 completed or ongoing studies (Table 54 and Table 55) evaluating avibactam alone and in combination with ceftazidime. Safety data from the two Phase 2 studies of CAZ-AVI in cIAI and cUTI are the focus of this clinical safety overview, supported by data from 11 Phase 1 Clinical Pharmacology studies evaluating CAZ-AVI or avibactam alone in healthy subjects and subjects with renal impairment. These data reinforce the nonclinical toxicology findings and reveal no new safety concerns associated with the administration of CAZ-AVI or avibactam alone. Interim safety data from 3 ongoing Clinical Pharmacology studies and 5 ongoing Phase 3 efficacy and safety studies provide further supportive information on the clinical safety of CAZ-AVI. The cumulative clinical safety data indicate that CAZ-AVI, administered at the proposed dose of 2.5 g IV q8h, has an acceptable safety profile consistent with that established for ceftazidime and the cephalosporin class.

In support of this 505(b)(2) NDA, safety information from the global clinical experience with ceftazidime over the last 28 years was systematically reviewed, and any potential safety concerns for ceftazidime were considered relevant to CAZ-AVI. The FDA AERS Database, the most recent US FORTAZ® package insert (FORTAZ package insert, 2010) and European ceftazidime Summary of Product Characteristics (SmPC), and available ceftazidime safety information from contemporary randomized comparative studies of cIAI and cUTI were reviewed and compared to the safety findings from the CAZ-AVI clinical program to identify any new safety signals.

5.1 Nonclinical Toxicology

Ceftazidime is a marketed antibiotic that has been shown through an extensive nonclinical testing package to have a well-established safety profile. For avibactam alone, a comprehensive panel of toxicology studies has been performed and consisted of toxicity studies of up to 3 months in duration in rats and dogs, safety pharmacology, genetic toxicology, reproductive toxicology (male and female fertility in rats, embryo-fetal development in the rat and rabbit, pre-and postnatal development), immunotoxicology, local tolerance studies, and an in vitro phototoxicity study. The subchronic (3-month) animal toxicity studies show that avibactam is generally well-tolerated and without associated target organ toxicity at exposures up to 3 and 6 times greater than exposures at the maximum recommended human dose (MRHD) of 0.5 g q8h (based on AUC) in rats and dogs, respectively. Reproductive studies were performed with avibactam during early pregnancy in rats and rabbits at doses that resulted in exposure multiples of 9 and 2 times, respectively, the exposure in humans at the MRHD. Slight maternal toxicity (characterized by reduced body-weight gain and food consumption), but no fetal toxicity was observed in rats. In rabbits, slightly higher post implantation loss and lower mean fetal weight, with slightly delayed ossification, were observed. In a pre- and postnatal toxicity study in rats, no effects on pup growth or viability were observed. A slight increase in renal pelvic dilatation and ureter dilatation was observed at doses of 3 times or greater the exposure in humans at the MRHD, but was not associated with pathological changes to renal parenchyma and therefore not considered adverse. This finding was also noted in control animals at a similar incidence as in the low-dose (No-observed-adverse-effect-level), which was equal to the MRHD.

The nonclinical program for CAZ-AVI was based on current international regulatory guidelines [ICHM3 (R2)], as well as the previously conducted individual nonclinical programs for ceftazidime and avibactam. Due to the short duration of clinical treatment (up to 14 days), one-month toxicity studies in rats and dogs with CAZ-AVI were conducted using a ratio of 4:1 (CAZ:AVI), which corresponds to the dose ratio intended for clinical use. Considering the established safety profile of ceftazidime and the absence of nonclinical safety concerns for avibactam, no combination genetic or reproductive toxicology studies were conducted. Carcinogenicity studies were also not conducted because of the proposed short-term treatment for bacterial infections with CAZ-AVI.

Overall, with the exception of a slight increase in local injection-site intolerance observed with ceftazidime in combination with avibactam as compared to ceftazidime alone, these studies support the safe use of CAZ-AVI as there were no new or unexpected toxicological findings in rats or dogs when both drugs were administered in combination in comparison to the effects observed from each individual agent.

5.2 Safety of Avibactam and CAZ-AVI

5.2.1 Exposure to CAZ-AVI or Avibactam Alone

The global clinical development safety database consists of 1896 subjects treated with CAZ-AVI or avibactam alone in 13 completed (Table 54) and 8 ongoing (Table 55) studies. The CAZ-AVI Safety Population includes all subjects who received any amount of study drug.

Subjects receiving CAZ-AVI or avibactam alone include 521 subjects in completed Phase 1 Clinical Pharmacology (352 subjects) and Phase 2 (169 subjects) studies (Table 54) and 1375 subjects in ongoing Phase 1 and Phase 3 studies (Table 55) as of an interim data cutoff date for the 120-day safety update report (15 Jun 2104). Thirty percent of subjects in the completed studies were enrolled in the US.

In the completed Phase 1 and Phase 2 studies, 286 adult subjects were treated with the proposed labeled dose of CAZ-AVI (2.5 g) or avibactam (0.5 g), 146 of whom (45 Phase 1 and 101 Phase 2) received study drug for 5-14 days. With the exception of a single-dose pediatric pharmacokinetic study, all ongoing CAZ-AVI studies are evaluating CAZ-AVI 2.5 g IV q8h infused over 2 h for 5 or more days, depending on the indication. As of the interim data cutoff date for the 120-day safety update report (15 Jun 2104), 1351 subjects in the ongoing studies at the time of NDA submission have received this proposed labeled dose regimen.

Table 54. Exposure to Study Drug in Completed CAZ-AVI Development Studies

Study ID	*Phase*	*Study Type*	*Total Enrolled N*	*AVI or CAZ-AVI n (rec. dose)*[a]	*Comparator and/or Placebo*[b] *n*	*AVI n (rec. dose)*[a]	*CAZ-AVI n (rec. dose)*[a]
NXL104/1001[c]	1	SD escalation PK	70	56 (16)	14	56 (8)	16 (8)
NXL104/1002	1	MD escalation PK	49	41 (24)	8	33 (16)	8 (8)
NXL104/1003	1	SD PK avibactam, renal impairment	31	31 (0)	0	31 (0)	0
NXL104/1004	1	SD PK avibactam, age and gender	33	33 (33)	0	33 (33)	0
D4280C00007	1	Thorough QT	51	46 (0)	47	0	46 (0)
D4280C00008	1	Distribution, metabolism, and excretion	6	6 (6)	0	6 (6)	0
D4280C00009	1	ELF	45	43 (22)	0	0	43 (22)
D4280C00010	1	SD and MD PK, Japanese subjects	16	13 (13)	3	6 (6)	7 (7)
D4280C00011[c]	1	DDI PK, ceftazidime and avibactam	43	43 (43)	27	27 (27)	43 (43)
D4280C00012[d]	1	DDI PK, metronidazole	28	28 (28)	27	0	28 (28)
CXL-PK-01[e]	1	DDI PK, ceftaroline and avibactam	60	12 (0)	0	12 (0)	0
NXL104/2001	2	Complicated urinary tract infections	137	68 (0)	67	0	68 (0)
NXL104/2002[d]	2	Complicated intra-abdominal infections	204	101 (101)	102	0	101 (101)
		Total Subjects	**773**	**521 (286)**	**295**	**204 (96)**	**360 (217)**

Abbreviations: AVI = avibactam; CAZ = ceftazidime; CXL = ceftaroline fosamil-avibactam; DDI = drug-drug interaction; DME = distribution, metabolism, and excretion; ELF = epithelial lining fluid; MD = multi-dose; MTZ = metronidazole; PK = pharmacokinetic; Rec. = recommended; QT = QT interval, SD = single-dose.

a AVI 0.5 g or CAZ-AVI 2.5 g (2 g CAZ + 0.5 g AVI) in single or multiple dose regimens, 2 h or shorter infusion times

b Comparators included moxifloxacin (D4280C00007), ceftazidime (D4280C00011), metronidazole (D4280C00012), imipenem (NXL104/2001), meropenem (NXL104/2002); Placebo controlled studies: NXL104/1001, NXL104/1002, D4280C00007, and D4280C00010.

c Subjects in crossover studies NXL104/1001 and D4280C00011 are counted in both the CAZ-AVI and AVI treatment groups but counted only once in the total receiving either drug. Twenty-seven subjects in Study D4280C00011 also received ceftazidime alone.

d Subjects in crossover Study D4280C00012 received both CAZ-AVI and CAZ-AVI + MTZ and are counted only once in the CAZ-AVI treatment group. Subjects in Study NXL104/2002 received CAZ-AVI + MTZ.

e Includes subjects who received CXL, ceftaroline fosamil, or AVI alone. Only subjects who received AVI alone are included in CAZ-AVI safety analyses.

Table 55. Ongoing Studies Supporting the CAZ-AVI Development Program

Study ID	*Phase*	*Study Type*	*Status*	*Double Blinded*	*N (randomized[a])*	*n (CAZ-AVI[b])*
D4280C00001/5	3	noninferiority: cIAI	ongoing	yes	1057	528
D4280C00002/4	3	noninferiority: cUTI	ongoing	yes	903	451
D4280C00006	3	open label Resistant Pathogen study: cIAI and cUTI	ongoing	no	222	113
D4280C00018	3	noninferiority: cIAI (Asia)	ongoing	yes	250	125
D4281C00001	3	noninferiority: HABP/VABP	ongoing	yes	217	109
D4280C00014	1	open label single-dose pediatric PK	ongoing	no	24	24
D4280C00020[c]	1	single- and multiple-dose PK (China)	ongoing	yes	16	12
D4280C00023[d]	1	open label multiple-dose, effect on intestinal flora (CAZ-AVI and CXL)	ongoing	no	13	13
				Total Subjects[a]	**2702**	**1375**

Abbreviations: CXL = ceftaroline fosamil-avibactam; HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; N = number of subjects enrolled; n (CAZ-AVI) = number of subjects exposed to CAZ-AVI.

a. Includes subjects enrolled in the ongoing studies as of 15 Jun 2014.

b. For blinded studies, includes estimated CAZ-AVI exposed based on 1:1 randomization, except for study D4280C00020 which randomized subjects 3:1 CAZ-AVI:placebo.

c. Ongoing at the time of NDA submission but has recently been completed.

d. Only safety data from subjects receiving CAZ-AVI in Study D4280C00023 are included in the safety analyses.

5.2.1.1 Clinical Pharmacology Studies

The 11 Phase 1 Clinical Pharmacology studies included treatment arms evaluating CAZ-AVI with and without MTZ, avibactam alone, ceftazidime alone and placebo groups. Healthy volunteers and subjects from special populations (ie, mild, moderate and severe renal impairment [including ESRD] and elderly subjects) received avibactam alone in doses ranging from 50 mg to 2000 mg, in single or multiple dose regimens, and CAZ-AVI in doses ranging from 1.25 g (1 g ceftazidime + 0.25 mg avibactam) up to 5 g (3 g ceftazidime + 2 g avibactam) in single or multiple dose regimens.

A subset of 31 subjects in the Clinical Pharmacology studies received CAZ-AVI at the dose and approximate dose regimen proposed for labeling as 2.5 g IV q8h for 10 days, 9.5 days, or 4.5 days (studies NXL104/1002, D4280C00011, or D4280C00010, respectively) over a 2 h or shorter infusion time. Fourteen subjects in these studies received 0.5 g avibactam alone at a duration of 4.5 days or longer.

5.2.1.2 Phase 2 Studies

In the Phase 2 cIAI study, a total of 101 subjects received CAZ-AVI + MTZ and 102 subjects received meropenem (Table 54). The median duration of CAZ-AVI or meropenem therapy was 6.0 and 6.5 days, respectively. No subject received > 14 days of study therapy. The majority of subjects in both treatment arms, including 94% of subjects in the CAZ-AVI + MTZ group and 94% subjects in the meropenem group, received the protocol specified dose regimen of CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 mg avibactam) + 0.5 g MTZ or 1 g meropenem q8h for 5 to 14 days.

In the Phase 2 cUTI study, a total of 68 subjects received CAZ-AVI (Table 54) and 67 subjects received imipenem. Most subjects in the CAZ-AVI and imipenem groups received 4 to 14 calendar days of study drug (IV plus oral therapy). The median duration of study drug therapy in the CAZ-AVI group was 11 days and in the imipenem group was 12 days. For IV study therapy alone, the median duration of CAZ-AVI therapy was 5 days and the median duration of imipenem therapy was 6 days. No subject received > 14 days of IV therapy. The median duration of oral therapy was 5 days in the CAZ-AVI group and 6 days in the imipenem group.

The majority of subjects in both treatment groups (88% CAZ-AVI, 84% imipenem) received the protocol-specified dose regimen CAZ-AVI 0.625 g (0.5 g ceftazidime + 0.125 g of avibactam) q8h or imipenem 0.5 g q6h for a minimum of 4 to a maximum of 14 days IV therapy.

The Safety Population demographic characteristics in the Phase 2 studies were similar to those presented for the mMITT Population (cIAI Section 4.5.1.3 and cUTI Section 4.5.2.3) and were balanced between the CAZ-AVI and comparator groups in both studies.

5.2.1.3 Ongoing Studies

As of an interim data cut of 15 Jun 2014, an estimated 1375 subjects in the ongoing studies at the time of NDA submission, most of which remain blinded, have received CAZ-AVI. This includes 162 subjects receiving CAZ-AVI in the open label Phase 1 and 3 studies, 12 subjects in Study D4280C00020 (based on 3:1 randomization) and 1326 subjects in the Phase 3 studies (based on 1:1 randomization to CAZ-AVI or comparator) (Table 56). Of these, approximately 1351 have received CAZ-AVI at the proposed labeled dose regimen.

Table 56. Enumeration of Subjects in Ongoing CAZ-AVI Studies - Safety Population

Study Number	*Number of Subjects*[a]		
	CAZ-AVI	*Comparator*	*Blinded*
Clinical Pharmacology Studies			
D4280C00014	24	—	—
D4280C00020[b]	12	4	—
D4280C00023[c]	13	—	—
Total Subjects: Phase 1	49	4	0
Phase 3 Studies			
D4281C00001 (HABP/VABP)	—	—	217
D4280C00001/5 (cIAI)	—	—	1057
D4280C00002/4 (cUTI)	—	—	903
D4280C00006 (cIAI and cUTI)	113	109	—
D4280C00018 (cIAI)	—	—	250
Total Subjects: Phase 3	113	109	2427
Total	**162**	**113**	**2427**

Abbreviations: CXL = ceftaroline fosamil-avibactam; HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

a Includes subjects randomized as of 15 Jun 2014.

b Includes 12 subjects in the CAZ-AVI group and 4 subjects in the placebo group..

c Study ongoing at the time of NDA submission, but recently completed.

5.2.2 Overview of Adverse Events

The overall incidence of TEAEs, SAEs, discontinuations of study drug due to TEAEs, and deaths were similar between treatment groups in each of the Phase 2 studies (Table 57).

Table 57. Summary of Adverse Events by Treatment Group, Phase 2 Studies — Safety Population

	cIAI NXL104/2002		*cUTI NXL104/2001*	
Subjects with:	*CAZ-AVI + MTZ (N = 101) n (%)*	*Meropenem (N = 102) n (%)*	*CAZ-AVI (N = 68) n (%)*	*Imipenem (N = 67) n (%)*
Any TEAE	65 (64.4)	59 (57.8)	46 (67.6)	51 (76.1)
Death	3 (3.0)*	2 (2.0)	0	1 (1.5)
Any SAE	9 (8.9)	11 (10.8)	6 (8.8)	2 (3.0)
Discontinuation of study drug due to TEAE	5 (5.0)	3 (2.9)	2 (2.9)	0

*One death in the CAZ-AVI group (cIAI) was reported after the end of the study (Day 67).

Across studies in the CAZ-AVI development program, safety data collected included adverse events (including any TEAEs, SAEs, TEAEs with outcomes of death, and TEAEs resulting in discontinuation of study drug), withdrawals from the study, laboratory parameters (including baseline and on-study chemistry, hematology, and coagulation panels), and vital signs. Electrocardiograms were performed and analyzed as part of the clinical safety database in order to confirm the findings of a negative Phase 1 thorough QT study. Additional analyses of TEAEs and clinical laboratory data were performed to investigate the potential for renal and hepatic toxicity or the potential for anemia, leukopenia, thrombocytopenia, hypersensitivity, and diarrhea (ie, adverse events of special interest [AEoSI]).

For the ongoing studies, the majority of which remain blinded, a descriptive summary of interim safety is provided for drug exposure, deaths, SAEs, and TEAEs resulting in discontinuation of study drug.

Table 58 provides a summary of adverse events for subjects enrolled in the open label Phase 3 Resistant Pathogen study as of the interim data cutoff date for the 120-day safety update (15 Jun 2014).

Table 58. Summary of Adverse Events by Treatment Group, Open-label Phase 3 Resistant Pathogen Study D4280C00006 — Safety Population

Subjects with:	***CAZ-AVI ± MTZ (N = 113) n (%)***	***BAT (N = 109) n (%)***
Death	3 (2.7)	3 (2.8)
Any SAE	8 (7.1)	7 (6.4)
Discontinuation of study drug due to TEAE	1 (0.9)	2 (1.8)

Abbreviations: BAT = best available therapy; CAZ-AVI = ceftazidime-avibactam; MTZ = metronidazole.

5.2.2.1 Common Adverse Events

In the pooled analyses for the Phase 1 Clinical Pharmacology studies, direct comparisons of adverse events rates across treatment groups are limited by the variable dose regimens and small sample sizes in some treatment groups (Table 56). Across all studies, no individual TEAE occurred in more than 15% of subjects, TEAEs were generally mild across all treatment groups, and no TEAE was assessed as severe. No deaths or SAEs occurred in any Phase 1 Clinical Pharmacology study. One subject was prematurely discontinued from treatment with high dose CAZ-AVI (5 g [3 g ceftazidime plus 2 g avibactam]) due to a TEAE (urticaria), possibly representing a hypersensitivity reaction.

Safety data for the avibactam and CAZ-AVI treatment groups is presented below.

5.2.2.1.1 Avibactam (Alone) Safety - Clinical Pharmacology

In the completed Clinical Pharmacology studies, healthy volunteers and subjects from special populations (ie, mild, moderate and severe renal impairment) received avibactam alone and in combination with ceftazidime in single and multiple dose regimens. The overall incidence of adverse events (Table 59) in the subjects receiving avibactam was generally lower than that observed with CAZ-AVI. The higher incidence of adverse events in the subjects from the Special Population group that received avibactam alone likely represents the higher incidence for adverse events one would expect overall in a special population with underlying co-morbidities (eg, severe renal impairment).

Adverse events observed in ≥ 2% of subjects in either the pooled avibactam or CAZ-AVI treatment groups in the completed Clinical Pharmacology studies are presented in Table 59. The most frequent adverse events in all subjects receiving avibactam alone were headache, diarrhea, and application site bruise and for CAZ-AVI were headache, urine odor abnormal, and diarrhea. The majority of adverse events were mild and none were reported to be severe.

Table 59. Adverse Events with an Incidence ≥ 2 for Subjects Receiving Avibactam Alone or CAZ-AVI, Clinical Pharmacology Studies — Safety Population

	CAZ-AVI	***Avibactam Alone***		
Preferred term	***Healthy Population (N = 191) n (%)***	***Healthy Population (N = 163) n (%)***	***Special Population (N = 41) n (%)***	***Total (N = 204) n (%)***
Headache	15 (7.9)	7 (4.3)	0	7 (3.4)
Urine odor abnormal	10 (5.2)	1 (0.6)	0	1 (0.5)
Diarrhea	7 (3.7)	3 (1.8)	1 (2.4)	4 (2.0)
Dermatitis contact	6 (3.1)	1 (0.6)	0	1 (0.5)
Back pain	5 (2.6)	0	0	0
Catheter site pain	4 (2.1)	0	0	0
Influenza like illness	4 (2.1)	0	0	0
Application site bruise	0	1 (0.6)	3 (7.3)	4 (2.0)
Dysgeusia	0	0	2 (4.9)	2 (1.0)
Fatigue	0	0	2 (4.9)	2 (1.0)

Abbreviations: CAZ-AVI = ceftazidime-avibactam; TEAE = treatment-emergent adverse event.

In summary, based on the completed Clinical Pharmacology studies, the safety profile for avibactam appears favorable.

5.2.2.1.2 Phase 2 Studies

In the Phase 2 cIAI study in which CAZ-AVI subjects received the proposed, labeled dose, 2.5 g IV q8h, the incidence of TEAEs was similar in the CAZ-AVI + MTZ and meropenem treatment groups (64.4% vs. 57.8%, respectively). The most common TEAEs (occurring in 8.9% to 13.9% of subjects) in the CAZ-AVI + MTZ group were vomiting, nausea, AST increased, blood alkaline phosphatase increased, and pyrexia. The most common TEAEs in the meropenem group (occurring in 6.9% to 14.7% of subjects) were AST increased, ALT increased, pyrexia, blood alkaline phosphatase increased, and platelet count increased (Table 60). Most TEAEs were mild or moderate in severity. No individual severe TEAE occurred in more than 2 (2.0%) subjects in either treatment group.

In the Phase 2 cUTI study (CAZ-AVI at lower than proposed, labeling dose, 0.625 g IV q8h), the incidences of TEAEs were also similar in the CAZ-AVI and the imipenem groups (67.6% vs. 76.1%, respectively). Most common TEAEs (occurring in 10.3% to 19.1% of subjects) in the CAZ-AVI group were headache, anxiety, and constipation. The most common TEAEs (occurring in 10.4% to 31.3% of subjects) in the imipenem group were headache, diarrhea, and anxiety. Most TEAEs were mild or moderate in severity. No individual severe TEAE was reported for >1 (1.5%) subject in either treatment group.

Table 60. TEAEs Reported in ≥ 5% Subjects Treated with CAZ-AVI in Either Phase 2 Study – Safety Population

System Organ Class *Preferred Term*	*cIAI*		*cUTI*	
	CAZ-AVI + MTZ (N = 101) n (%)	*Meropenem (N = 102) n (%)*	*CAZ-AVI (N = 68) n (%)*	*Imipenem (N = 67) n (%)*
Gastrointestinal disorders				
Abdominal pain	8 (7.9)	3 (2.9)	5 (7.4)	3 (4.5)
Abdominal pain upper	1 (1.0)	0	5 (7.4)	1 (1.5)
Constipation	4 (4.0)	1 (1.0)	7 (10.3)	2 (3.0)
Diarrhea	5 (5.0)	4 (4.9)	6 (8.8)	7 (10.4)
Nausea	10 (9.9)	6 (5.9)	0	2 (3.0)
Vomiting	14 (13.9)	5 (4.9)	0	0
General disorders and administration site conditions				
Chest pain	1 (1.0)	1 (1.0)	4 (5.9)	3 (4.5)
Pyrexia	9 (8.9)	11 (10.8)	0	1 (1.5)
Investigations				
Alanine aminotransferase increased	8 (7.9)	13 (12.7)	2 (2.9)	4 (6.0)
Aspartate aminotransferase increased	9 (8.9)	15 (14.7)	2 (2.9)	3 (3.4)
Blood alkaline phosphatase increased	9 (8.9)	7 (6.9)	2 (2.9)	1 (1.5)
White blood cell count increased	5 (5.0)	6 (5.9)	0	0
Nervous system disorders				
Headache	3 (3.0)	3 (2.9)	13 (19.1)	21 (31.3)
Dizziness	0	2 (2.0)	4 (5.9)	0
Psychiatric disorders				
Anxiety	5 (5.0)	1 (1.0)	7 (10.3)	5 (7.5)
Insomnia	0	2 (2.0)	4 (5.9)	4 (6.0)
Renal and urinary disorders				
Pyuria	5 (5.0)	5 (4.9)	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (5.9)	4 (3.9)	1 (1.5)	1 (1.5)
Vascular disorders				
Hypertension	2 (2.0)	3 (2.9)	4 (5.9)	2 (3.0)

Abbreviation: MTZ = metronidazole.

5.2.2.2 Deaths

No death occurred in any completed or ongoing Clinical Pharmacology study. In the Phase 2 and ongoing Phase 3 studies, deaths occurred in small numbers in any treatment group and no apparent association with study drug was observed.

In the cumulative CAZ-AVI safety database, 61 deaths have been reported, including 7 deaths in the Phase 2 studies and 54 deaths in the ongoing Phase 3 studies as of the interim data cutoff date of 15 Jun 2014. In the Phase 2 studies 6 deaths occurred during the study period (3 CAZ-AVI, 3 comparator; Table 61). One additional death (CAZ-AVI) was reported after the study. None of the deaths in any study were assessed by the investigator or Sponsor to be caused by study drug. The causes of death were consistent with those expected for the population enrolled in these studies.

Table 61. Causes of Death for Subjects in Phase 2 Studies—Safety Population

Subject ID	*Preferred Term*	*System Organ Class*	*Relationship to Study Drug*	*Study Day of Death*
NXL104/2002 cIAI, CAZ-AVI + MTZ group				
32001[a]	Septic shock	Infections and infestations	Unrelated	67
42005	Multiple organ failure	General disorders and administration site conditions	Unrelated	13
67001	Sepsis	Infections and infestations	Unrelated	20
72003	Cardiac arrest	Cardiac disorders	Unrelated	2
NXL104/2002 cIAI, meropenem group				
23004	Peritonitis	Gastrointestinal disorders	Unrelated	5
63006	Pneumonia	Infections and infestations/ Pneumonia	Unrelated	8
	Platelet count decreased	Investigations	Unrelated	8
NXL104/2001 cUTI, CAZ-AVI group				
N/A	—	—	—	—
NXL104/2001 cUTI, imipenem group				
20304	Urosepsis	Infections and infestations	Unrelated	46

Abbreviations: ID = identifier; MTZ = metronidazole; N/A = not applicable; SAE = serious adverse event.
a Subject NXL104/2002-32001 died after study discontinuation.

In the ongoing open-label Phase 3 Resistant Pathogen study, 6 deaths have been reported (3 CAZ-AVI, 3 BAT comparator). None of the deaths in either treatment group were assessed by the Investigator or the Sponsor to be related to study drug.

5.2.2.3 Serious Adverse Events

No SAEs have been reported in the completed or ongoing Clinical Pharmacology studies.

SAEs reported in the completed Phase 2 studies are presented in Table 62. No SAE occurred in more than 2 subjects in any treatment group in either study. Five subjects, 1 in the cIAI study (CAZ-AVI + MTZ group) and 4 in the cUTI study (3 in the CAZ-AVI group and 1 in the imipenem group) had SAEs considered related to study drug (hepatic enzyme increased; diarrhea; accidental overdose; renal failure, acute; and blood creatinine, increased). Two of these 5 SAEs, both in the CAZ-AVI (± MTZ) group led to premature discontinuation of study drug (hepatic enzyme increased and accidental overdose, defined per protocol as a serious event).

The SAE of hepatic enzyme increased occurred in a subject with cholecystitis with serum alkaline phosphatase increasing disproportionately to the transaminase elevations. The SAE of diarrhea occurred in a subject with constipation on concurrent opiate therapy who subsequently developed diarrhea after receiving magnesium and bisacodyl; *Clostridium difficile* toxin was negative. The event was moderate in severity and was an SAE due to prolongation of hospitalization. The SAE of accidental overdose occurred in a subject who was given a single dose CAZ-AVI 2.5 g instead of the protocol dose of 0.625 g; the overdose was not associated with symptoms and was considered an SAE based on protocol requirement. The SAE of acute renal failure occurred in a subject with a history of a kidney transplant, hypertension, nephrolithiasis, and recurrent UTI; serum creatinine increased from 0.8 mg/dL to 2.3 mg/dL. On follow up, the SAE had resolved with sequelae.

Table 62. Incidence of Treatment-Emergent Serious Adverse Events by Treatment Group, System Organ Class and Preferred Term in Phase 2 Studies — Safety Population

	cIAI NXL104/2002		***cUTI NXL104/2001***	
System Organ Class Preferred Term	***CAZ-AVI + MTZ (N = 101) n (%)***	***Meropenem (N = 102) n (%)***	***CAZ-AVI (N = 68) n (%)***	***Imipenem (N = 67) n (%)***
Any serious adverse event	9 (8.9)	11 (10.8)	6 (8.8)	2 (3.0)
Cardiac disorders	1 (1.0)	1 (1.0)	1 (1.5)	0
Atrial fibrillation	0	1 (1.0)	1 (1.5)	0
Cardiac arrest	1 (1.0)	0	0	0
Gastrointestinal disorders	4 (4.0)	3 (2.9)	1 (1.5)	0
Gastric perforation	1 (1.0)	0	0	0
Intestinal obstruction	1 (1.0)	2 (2.0)	0	0
Localized intraabdominal fluid collection	1 (1.0)	0	0	0
Peritonitis	0	1 (1.0)	0	0
Volvulus	1 (1.0)	0	0	0
Diarrhea	0	0	1 (1.5)	0
General disorders and administration site conditions	1 (1.0)	0	0	0
Multi-organ failure	1 (1.0)	0	0	0

Table 62. **Incidence of Treatment-Emergent Serious Adverse Events by Treatment Group, System Organ Class and Preferred Term in Phase 2 Studies — Safety Population**

	cIAI NXL104/2002		*cUTI NXL104/2001*	
System Organ Class ***Preferred Term***	***CAZ-AVI + MTZ (N = 101) n (%)***	***Meropenem (N = 102) n (%)***	***CAZ-AVI (N = 68) n (%)***	***Imipenem (N = 67) n (%)***
Infections and infestations	4 (4.0)	2 (2.0)	0	1 (1.5)
Pneumonia	1 (1.0)	1 (1.0)	0	0
Postoperative abscess	1 (1.0)	1 (1.0)	0	0
Sepsis	1 (1.0)	0	0	0
Septic shock	1 (1.0)	0	0	0
Urosepsis	0	0	0	1 (1.5)
Injury, poisoning and procedural complications	0	1 (1.0)	1 (1.5)	0
Wound secretion	0	1 (1.0)	0	0
Accidental overdose	0	0	1 (1.5)	0
Investigations	1 (1.0)	1 (1.0)	0	1 (1.5)
Blood creatinine increased	0	0	0	1 (1.5)
Hepatic enzyme increased	1 (1.0)	0	0	0
Platelet count decreased	0	1 (1.0)	0	0
Metabolism and nutrition disorders	0	1 (1.0)	0	0
Diabetes mellitus	0	1 (1.0)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (1.5)	0
Intervertebral disc protrusion	0	0	1 (1.5)	0
Renal and urinary disorders	0	1 (1.0)	2 (2.9)	0
Renal failure acute	0	1 (1.0)	1 (1.5)	0
Renal impairment	0	0	1 (1.5)	0
Respiratory, thoracic and mediastinal disorders	1 (1.0)	2 (2.0)	0	0
Respiratory disorder	0	1 (1.0)	0	0
Respiratory distress	1 (1.0)	0	0	0
Tracheo-oesophageal fistula	0	1 (1.0)	0	0

Abbreviation: MTZ = metronidazole.

NOTE: Serious adverse events are coded using MedDRA Version 11.1 or higher

In the ongoing blinded Phase 3 studies, 228 SAEs have been reported in 183 subjects (6.8 %) as of the interim data cutoff. Within each study, each SAE preferred term occurred in ≤ 2 subjects.

In the only open-label Phase 3 study (Resistant Pathogen Study D4280C00006), 8 SAEs were reported in 8 of the 113 subjects treated with CAZ-AVI, and 8 SAEs were reported in 7 of the 109 subjects treated with a BAT comparator. None of the SAEs in either treatment group were considered by the investigator to be related to study drug. In the blinded ongoing Phase 3 studies, 6 SAEs were considered related to study drug including: transaminases increased, drug eruption, hypersensitivity, pyrexia, increased ALT, and increased AST. None of the SAEs related to liver enzyme elevations met Hy's Law criteria or resulted in liver failure. For each of the indications under study, the incidences of SAEs in the ongoing Phase 3 studies are comparable to those from the completed Phase 2 studies and/or relevant literature.

5.2.2.4 Adverse Events Leading to Premature Discontinuation of Study Drug or Withdrawal from Study

One subject was prematurely discontinued from study drug in a Clinical Pharmacology study due to a non-serious TEAE (urticaria).

TEAEs leading to premature discontinuation of study drug in the Phase 2 studies are presented in Table 63. One additional subject discontinued study drug due to an adverse event (rash, generalized) erroneously reported as non-treatment emergent. Other than the 3 subjects who discontinued study drug due to TEAEs representing rash, no single TEAE leading to premature discontinuation of study drug occurred in >1 subject.

Table 63. Treatment-Emergent Adverse Events Resulting in Discontinuation of Study Drug by Treatment Group, System Organ Class and Preferred Term, in Phase 2 Studies — Safety Population

	cIAI NXL104/2002		*cUTI NXL104/2001*	
System Organ Class ***Preferred Term***	***CAZ-AVI + MTZ (N = 101) n (%)***	***Meropenem (N = 102) n (%)***	***CAZ-AVI (N = 68) n (%)***	***Imipenem (N = 67) n (%)***
Any TEAE resulting in treatment discontinuation	5 (5.0)	3 (2.9)	2 (2.9)	0
Cardiac disorders	1 (1.0)	0	1 (1.5)	0
Atrial fibrillation (SAE)	0	0	1 (1.5)	0
Cardiac arrest (SAE)	1 (1.0)	0	0	0
Gastrointestinal disorders	1 (1.0)	0	0	0
Nausea	1 (1.0)	0	0	0
Vomiting	1 (1.0)	0		
Infections and infestations	1 (1.0)	1 (1.0)	0	0
Pneumonia (SAE)	0	1 (1.0)	0	0
Septic shock (SAE)	1 (1.0)	0	0	0
Injury, poisoning and procedural complications	0	0	1 (1.5)	0
Accidental overdose (SAE)	0	0	1 (1.5)	0
Investigations	1 (1.0)	1 (1.0)	0	0
Hepatic enzyme increased (SAE)	1 (1.0)	0	0	0
Platelet count decreased (SAE)	0	1 (1.0)	0	0
Nervous system disorders	0	1 (1.0)	0	0
Dizziness	0	1 (1.0)	0	0
Headache	0	1 (1.0)	0	0
Psychiatric disorders	1 (1.0)	0	0	0
Anxiety	1 (1.0)	0	0	0
Renal and urinary disorders	0	1 (1.0)	0	0
Renal failure acute (SAE)	0	1 (1.0)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (1.0)	0	0
Dyspnoea	0	1 (1.0)	0	0
Skin and subcutaneous tissue disorders	2 (2.0)*	0	0	0
Rash macular	1 (1.0)	0	0	0
Rash pruritic	1 (1.0)	0	0	0

*An additional CAZ-AVI subject (cIAI) had a rash that was erroneously reported as a non-TEAE.

In the ongoing studies, 46 subjects prematurely discontinued study drug due to a TEAE. The most common TEAE resulting in premature discontinuation across all ongoing Phase 3 studies was drug eruption, occurring in 3 subjects (0.2%) across the 5 Phase 3 studies; otherwise, each TEAE preferred term leading to premature discontinuation occurred in no more than 2 subjects in any study. In the open-label Resistant Pathogen study (D4280C00006), 2 subjects in the BAT comparator group prematurely discontinued study drug due to a TEAE. One subject had lobar pneumonia and the other had *C. difficile* colitis.

5.2.3 Analysis of Topics of Special Interest

MedDRA preferred terms were pre-identified for 5 topics of special interest: liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders, irrespective of whether the terms were observed in any CAZ-AVI clinical studies. Safety data from the completed Phase 1 and Phase 2 studies were then programmatically reviewed for these AEoSI to identify both adverse events (including any TEAEs, TEAEs with outcomes of death, SAEs, and TEAEs resulting in premature discontinuation of study drug) and PCS laboratory values representing potential safety concerns for these 5 topics of special interest.

These 5 topics of special interest were selected as they are relevant to the known safety profile of ceftazidime (eg, hypersensitivity) and/or other cephalosporins (eg, hematologic disorders representing low blood counts) or based on safety topics that are known to result in severe complications for any drug (eg, liver disorders). The incidence of subjects who experienced at least 1 preferred term within a given category and the incidence of each TEAE preferred term reported in the CAZ-AVI safety database are summarized.

5.2.3.1 Phase 1 Studies

Review of TEAEs and PCS laboratory values representing possible safety concerns for 5 topics of AEoSI demonstrated that clinically relevant safety events were uncommon in the Phase 1 Clinical Pharmacology studies. As previously noted, 1 subject in a completed Phase 1 study discontinued high-dose CAZ-AVI (5 g) due to a TEAE of urticaria (Section 5.2.2), representing a possibly hypersensitivity reaction. One subject with mild renal impairment in the renal impairment study (NXL104/1003) who received avibactam alone experienced a mild TEAE representing a possible renal disorder (CrCL decreased) that recovered and was considered unrelated to study drug. Four additional subjects receiving avibactam in the same study (NXL104/1003) had PCS increases in creatinine, although these subjects were all in the ESRD group and PCS creatinine elevations occurred between hemodialysis sessions. One subject receiving avibactam experienced a non-serious increase in hepatic enzymes, reported as a TEAE (transaminases increase) that was considered mild in severity and related to study drug. The subject did not prematurely discontinue study drug and the transaminase elevations did not meet laboratory criteria for potential Hy's Law.

5.2.3.2 Phase 2 Studies

Liver Disorders
In the Phase 2 studies, the incidences of subjects with TEAEs representing liver disorders were similar in the CAZ-AVI and comparator groups, occurring in 9.9% vs. 14.7%, respectively, in the Phase 2 cIAI study, and 4.4% vs. 7.5%, respectively, in the Phase 2 cUTI study. Across both Phase 2 studies there was 1 SAE representing liver disorders (hepatic enzyme increased) occurring in 1 subject on CAZ-AVI + MTZ in the Phase 2 cIAI study, who had elevations of AST, ALT (both 2 × ULN), and alkaline phosphatase (4.7 × ULN) assessed as moderate in severity, but resulting in prolonged hospitalization. The elevations resolved and bilirubin was never increased. Within each Phase 2 study, the incidences of subjects with postbaseline ALT or AST values > 3, 5, or 10 × ULN were low and similar in the CAZ-AVI and comparator groups. One subject in Phase 2 cIAI study in the meropenem group met laboratory criteria for potential Hy's Law but ultimately, no subject in either group met Hy's Law.

Diarrhea
No subjects discontinued study drug or died due to a TEAE representing diarrhea in the Phase 2 studies. The incidences of TEAEs representing potential antibiotic-associated diarrhea were similar in CAZ-AVI and comparator groups in the Phase 2 cIAI study (5.0% vs. 4.9%, respectively) and in the Phase 2 cUTI study (8.8% vs. 10.4%, respectively). In the Phase 2 studies, there were no cases of CDAD. CDAD has been reported in 3 subjects in the ongoing blinded Phase 3 studies. One subject treated with comparator in the open-label ongoing Resistant Pathogen study had a TEAE of *C. difficile* colitis. While diarrhea and more importantly CDAD can occur with most antibiotics, including ceftazidime, the risk of these adverse events following CAZ-AVI administration appears to be similar to that of the comparators studied and there have been no cases of CDAD among any CAZ-AVI-treated subjects.

Hypersensitivity
Across both Phase 2 studies, no TEAEs representing hypersensitivity/allergic reactions resulted in death or an SAE. No cases of anaphylaxis have been reported in the CAZ-AVI safety database to date. In the completed CAZ-AVI Phase 2 cIAI study, 3 TEAEs (rash pruritic, rash macular, and rash generalized) resulted in discontinuation of study drug in 3 subjects in the CAZ-AVI + MTZ group. There were no premature discontinuations due to TEAEs related to hypersensitivity in the comparator group and none in either group in the Phase 2 cUTI study. Thus, while allergic reactions can occur with most antibiotics, including other β-lactams, the risk of allergic reactions to CAZ-AVI was similar to that of the comparators studied (ie, carbapenems).

Hematologic Disorders
In the Phase 2 clinical studies, the incidences of TEAEs or PCS laboratory values representing possible anemia, thrombocytopenia, or leukopenia were low and similar in the CAZ-AVI and comparator groups. A positive Coombs' test is known to occur with administration of β-lactam antibiotics, with incidences as high as 16% for cefepime (Cefepime package insert, 2013). In the Phase 2 studies, the incidence of a positive Coombs' test was < 10% for both the CAZ-AVI and comparator groups; 7.3% vs. 2.4%, respectively in cIAI and 1.9% vs. 8.3%, respectively, in cUTI. None of these subjects had laboratory evidence of hemolysis or other TEAEs representing hematologic disorders.

Renal Disorders
In the CAZ-AVI clinical studies, the incidences of TEAEs and PCS postbaseline chemistry values representing possible renal disorders were low and similar in the CAZ-AVI and comparator groups. In the Phase 2 studies, the incidences of subjects with TEAEs representing renal disorders in the CAZ-AVI and comparator groups were 5.9% vs. 6.9%, respectively, in the cIAI study and 2.9% vs. 6.0%, respectively, in the cUTI study. In the Phase 2 cUTI study, 2 subjects in the CAZ-AVI group had SAEs representing renal disorders (acute renal failure, renal impairment). Both subjects had complicating renal comorbidities, neither SAE was severe, and both SAEs resolved without sequelae. In the Phase 2 cIAI study, an SAE of acute renal failure occurred in 1 subject in the meropenem group that led to premature discontinuation of study drug. PCS postbaseline creatinine elevations were rare in the Phase 2 studies, occurring in 1 subject in each study. One subject receiving CAZ-AVI + MTZ (cIAI) who died of multi-organ failure had a PCS creatinine elevation not reported as a TEAE, and 1 subject in the imipenem group (cUTI) had an SAE of increased blood creatinine.

5.2.4 Laboratory and Electrocardiogram Findings

Results of liver function tests, renal function tests, and hematology tests are summarized in Section 5.2.3. Safety concerns were not observed based on a systematic review of other routine chemistry, hematology, and coagulation data.

As reviewed in Section 4.3.2, results of a thorough QT study (D4280C00007) evaluating CAZ-AVI 5 g (3 g ceftazidime + 2 g avibactam) given as a 30-minute single infusion demonstrated that supratherapeutic doses of CAZ-AVI did not significantly prolong the QTcF at peak plasma concentration or at any other time. The largest 90% upper bound for the placebo corrected mean change from baseline was 5.9 msec. There were no QTcF intervals > 450 msec or QTcF interval changes from baseline > 30 msec.

In the Phase 2 studies, one CAZ-AVI-treated subject (cUTI study) and 1 meropenem-treated subject (cIAI study) each had 1 QTcF > 500 msec (and change from baseline > 60 msec) during the study. Both had a medical history of preexisting cardiac disease and neither experienced a cardiac TEAE associated with the QTcF prolongation.

5.3 POSTMARKETING EXPERIENCE WITH CEFTAZIDIME

In support of this 505(b)(2) NDA, safety information from the global clinical experience with ceftazidime over the last 28 years was systematically reviewed and assessed in aggregate, including US and European Union product labeling for ceftazidime, signal detection analysis using the FDA AERS database, and available ceftazidime safety information from contemporary randomized comparative studies of cIAI and cUTI.

5.3.1 Label Review

Safety information for ceftazidime from product information labels in the US and Europe (FORTAZ package insert, 2010; ceftazidime SmPC, 2014; FORTUM 1 g injection SmPC, 2013) were reviewed. All safety concerns currently considered associated with ceftazidime administration as adverse drug reactions (ADRs) and/or included as important cephalosporin class effects in the Warnings and Precautions section of the package insert were considered relevant to CAZ-AVI. This review identified 64 unique preferred terms associated with ceftazidime that were incorporated into the assessment of ADRs, warnings and precautions for the proposed product label for CAZ-AVI.

5.3.2 Signal Detection from the FDA AERS Database

Signal detection from the FDA AERS database for ceftazidime was evaluated to identify drug-event combinations (ceftazidime-Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term combinations) that were at least twice the expected reporting ratio relative to all other drug-event combinations (ie, $EB_{05} \geq 2$; Hauben et al, 2005). EB_{05} is the lower bound of the 90% CI for the geometric mean of the empirical Bayes posterior distribution of the relative reporting risk or Empirical Bayes Geometric Mean (EBGM). This methodology yielded 2 MedDRA Preferred Terms: Myoclonus and Status Epilepticus, which were evaluated by product label and published literature review.

Similar terms “myoclonia” and “seizures” are labeled in the current ceftazidime product information (FORTAZ package insert, 2010) under Warnings and Precautions with respect to elevated levels of ceftazidime in patients with renal impairment, noting the recommendation for dosing adjustment in patients with renal insufficiency. Seizures are noted as a central nervous system adverse drug reaction associated with the cephalosporin class, along with myoclonia in renally impaired patients with unadjusted dosing regimens of ceftazidime. Likewise, “seizure activity” is noted in the Overdose section as a potential reaction to ceftazidime in subjects with renal failure. The term “status epilepticus” does not appear in the current FORTAZ package insert or the ceftazidime or FORTUM SmPCs, although may be considered to be a type of seizure activity.

A review of relevant publications resulting from a search of the published literature for myoclonus and status epilepticus occurring in the setting of ceftazidime therapy was undertaken to determine whether these terms are appropriately characterized in the current ceftazidime label.

Both myoclonus and the status epilepticus subtype, nonconvulsive status epilepticus (NCSE), have been observed with concurrent ceftazidime therapy, most commonly in renally-impaired patients without proper dosage adjustment or as a result of overdose. However, NCSE may occur even in the presence of dosing adjustments recommended for patients with renal impairment. No cases of NCSE occurred in subjects receiving the recommended dosage of ceftazidime for the treatment of cIAI or cUTI. As a result of our safety review, it was determined that the term "myoclonus" is satisfactorily characterized in the current ceftazidime label as "myoclonia." However, given the nonconvulsive clinical presentation and requirement for electroencephalogram-guided diagnosis, a high grade of suspicion is necessary to diagnose NCSE secondary to ceftazidime administration in patients with renal impairment and altered consciousness or encephalopathy. Accordingly, the term is specifically noted in more recent cephalosporin labels (Cefepime Package Insert, 2013). As a result of this review, NCSE is proposed as a potential ADR for ceftazidime.

5.3.3 Literature Review of Ceftazidime in cIAI and cUTI

As summarized in Section 3.0, a systematic review of the literature and meta-analysis of historical comparative trials was conducted to provide supportive evidence of ceftazidime as an efficacious drug in the treatment of cIAI and cUTI. Available safety data from the final list of prospective, randomized, comparator-controlled studies in cIAI or cUTI were reviewed. Eighteen references provided information on adverse events occurring in the studies. All adverse events were consistent with the known safety profile of ceftazidime as outlined in the package inserts, and no new safety signals were identified.

6.0 BENEFIT/RISK SUMMARY

6.1 NONCLINICAL EVIDENCE THAT AVI EXTENDS CAZ ACTIVITY

Available nonclinical data, including in vitro and in vivo microbiology data, PK data, PK/PD target attainment, safety pharmacology data, and toxicology data—in addition to accumulated historical efficacy data for ceftazidime alone—provide a solid foundation that is predictive of CAZ-AVI's effectiveness in the treatment of patients with serious bacterial infections (including cIAI, cUTI and other infections with limited treatment options).

CAZ-AVI is rapidly bactericidal against a wide range of Gram-negative and Gram-positive pathogens, including aerobes and selected obligate and facultative anaerobes. Ceftazidime is currently approved for the treatment of serious bacterial infections caused by susceptible pathogens, including *Enterobacteriaceae* (*Enterobacter* spp., *Proteus* spp., *Klebsiella* spp., and *E. coli*), *P. aeruginosa*, and methicillin-susceptible *S. aureus* (FORTAZ package insert, 2010). Avibactam restores the potency of ceftazidime against CAZ-NS pathogens that produce Class A and Class C β-lactamases (eg, ESBLs, KPC carbapenemases, and AmpC enzymes) and some Class D enzymes. The in vitro antibacterial activity of CAZ-AVI against contemporary β-lactamase-producing organisms has been confirmed in surveillance studies conducted in the US and other geographic regions of the world. This broad spectrum of activity provides a benefit over currently available BL-BLI combinations (eg, piperacillin-tazobactam, ampicillin-sulbactam, and ticarcillin-clavulanic acid), as the activity of these older BLIs are limited to selected Class A enzymes (Endimiani et al, 2011; Livermore et al, 2008; Mushtaq et al, 2010; Robbins et al, 2005). In addition, unlike clavulanic acid, avibactam does not induce AmpC β-lactamase production at clinically relevant concentrations.

Animal infection models have demonstrated CAZ-AVI efficacy against Class A and Class C serine β-lactamase-producing bacteria, against which ceftazidime alone is ineffective. CAZ-AVI has demonstrated effective reduction in bacterial titers from the lungs in mouse pneumonia models, from the CSF in a rabbit meningitis model, and from the kidney in a mouse pyelonephritis model. Importantly, animal efficacy studies with CAZ-AVI provide in vivo evidence that avibactam restores the activity of ceftazidime against CAZ-NS bacteria that produce serine β-lactamases. The results from animal models were predictive of the efficacy that was observed for CAZ-AVI against CAZ-NS pathogens in the Phase 2 cUTI and cIAI trials as well as the Resistant Pathogen study.

6.2 CLINICAL BENEFITS

The predictable, linear PK of avibactam and ceftazidime provide important clinical benefits. No dose adjustment is needed for CAZ-AVI based on age or impaired hepatic function. Simple dose adjustment of CAZ-AVI, in alignment with that for ceftazidime alone, is recommended for patients with impaired renal function (CrCL < 50 mL/min). The potential for DDIs with CAZ-AVI is low; for example, no PK interactions were observed between avibactam and ceftazidime or between CAZ-AVI and MTZ. CAZ-AVI demonstrates no potential to prolong the QTc interval.

In subjects with cIAI, CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h for 5 to 14 days, in combination with MTZ (added for anaerobic coverage), demonstrated efficacy in treating cIAI caused by a variety of Gram-negative organisms in the Phase 2 cIAI study. In the primary efficacy analysis at TOC in the mMITT Population, favorable clinical response was high and consistent with estimates from contemporary Phase 3 cIAI clinical trials.

In subjects with cUTI, CAZ-AVI 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) IV q8h, with an optional oral switch to ciprofloxacin after a minimum of 4 days and a total therapy duration of 7 to 14 days, demonstrated efficacy in treating cUTI caused by CAZ-S and CAZ-NS *Enterobacteriaceae* uropathogens in the Phase 2 cUTI study. In the primary efficacy analysis at TOC in the mMITT Population, favorable microbiological outcome was similar between the CAZ-AVI and imipenem treatment groups and consistent with contemporary Phase 3 trials.

Among the 145 pooled subjects with infections caused by CAZ-NS pathogens who were enrolled in the two Phase 2 studies and the ongoing Resistant Pathogen Study, CAZ-AVI showed numerically higher favorable outcomes compared with the comparator group in treating cIAI and cUTI caused by CAZ-NS Gram-negative bacilli. The higher favorable microbiological response rate in the CAZ-AVI group was evident in the by-pathogen analyses as well.

Clinical experience with ceftazidime alone in indications other than cIAI and cUTI (such as bacteremia and nosocomial pneumonia)—coupled with the observed similarities between ceftazidime and avibactam PK properties and in vivo efficacy of CAZ-AVI vs. CAZ-NS pathogens (including animal models of bacteremia and pneumonia)—support the use of CAZ-AVI for additional MDR Gram-negative infections with limited treatment options. With respect to pneumonia, it was demonstrated that avibactam and ceftazidime can penetrate into ELF to a similar extent and with similar kinetics. Thus avibactam will be present at the site of infection to protect ceftazidime from β-lactamases. The dose selection for CAZ-AVI was ultimately based on target attainment simulations for cIAI subjects, who were predicted to have faster clearance and lower plasma levels, of both ceftazidime and avibactam compared to cUTI subjects or healthy subjects. The estimated clearance of ceftazidime for cIAI subjects from the population PK model (11.3 L/h) is greater than the estimate for ceftazidime clearance in nosocomial pneumonia patients (6.47 L/h) (Muller et al, 2013). Based on this observation, PTA in nosocomial pneumonia would be expected to be greater than the PTA estimated for simulated cIAI subjects. The proposed dose regimen for CAZ-AVI should therefore be appropriate for treating infections with limited treatment options including HABP/VABP (and bacteremia) where limited or no alternative therapies are available.

6.3 LIMITATIONS AND RISKS

CAZ-AVI is generally well tolerated and its safety profile is consistent with that of available systemic cephalosporins (including ceftazidime alone). The cumulative safety database in this submission consists of data from 21 completed or ongoing studies, including a total of 1896 subjects who have received CAZ-AVI, ceftazidime, or avibactam alone.

In the Phase 2 studies, the incidence of TEAEs was similar between the CAZ-AVI and carbapenem comparator groups, the majority of which were mild to moderate in severity (≤ 4% of CAZ-AVI-treated subjects in either study experienced severe TEAEs). Consistent with known β-lactam class effects, the most common TEAEs were gastrointestinal effects in both studies (approximately 25% in cIAI and 40% in cUTI). TEAEs rarely led to premature discontinuation of study drug. There was no trend in the specific SAEs reported and the events were as expected in subjects with cIAI and cUTI and no specific safety concerns were identified. Deaths during the study period were uncommon (3 in the CAZ-AVI group and 3 in comparator groups), and none were considered related to study drug.

Uncommon known and potential adverse reactions that are associated with the β-lactam class (eg, diarrhea, hypersensitivity, hematopoietic cytopenias, renal insufficiency, and rarely liver injury) were infrequently observed during the CAZ-AVI clinical studies. In the Phase 2 studies, < 10% of CAZ-AVI-treated subjects had any TEAEs representing potential liver disorders, and this incidence was lower than that observed in the comparator groups in both studies; no subject met Hy's Law. No subject discontinued study drug due to a TEAE representing diarrhea and no case of CDAD was reported in a CAZ-AVI-treated subject; the single SAE of diarrhea in the CAZ-AVI group of the Phase 2 cUTI study was associated with laxatives and was *C. difficile* toxin-negative. The incidences of subjects with TEAEs representing hypersensitivity were low and similar between treatment groups in both of the Phase 2 studies (≤ 6% each group), and none of these events represented anaphylaxis. Similarly, the incidences of subjects with TEAEs representing renal disorders were low and similar between treatment groups in both Phase 2 studies (≤ 7% each group). In the Phase 2 cUTI study, 2 subjects in the CAZ-AVI group had SAEs representing renal disorders (acute renal failure, renal impairment). Both subjects had complicating renal comorbidities, neither SAE was severe, and both resolved without sequelae.

The demonstrated safety in infected subjects treated with CAZ-AVI in the Phase 2 studies is supported by the well-characterized safety profile of ceftazidime alone. The totality of non-clinical and clinical data indicates that avibactam does not significantly alter the safety profile of ceftazidime. The safety of CAZ-AVI will be further reinforced with the completion of studies in the ongoing Phase 3 program, the supplemental NDA that will provide updated labeling, and post-marketing surveillance.

CAZ-AVI shows low propensity for resistance development against key pathogens as was demonstrated in spontaneous mutation studies. In a hollow-fiber model, rare mutants with a deletion in the Ω-loop of the AmpC β-lactamase were detected; however, this appears to be limited to in vitro experiments, and the proposed CAZ-AVI dose leads to in vivo conditions under which resistance selection is limited. The risk of emergence of resistant bacterial strains with widespread or inappropriate use of CAZ-AVI (eg, for minor illnesses) is also limited by the parenteral route of administration and the fact that subjects receiving CAZ-AVI for treatment of cIAI or cUTI will likely be in a medical facility and/or under the direct supervision of a healthcare provider.

With respect to the activity of CAZ-AVI against *P. aeruginosa*, none of the 5 subjects in the Phase 2 cUTI study who were infected with *P. aeruginosa* had a favorable microbiological response (3 CAZ-AVI subjects, CAZ-AVI MIC range of 2 to 4 mg/L; 2 imipenem subjects, imipenem MIC range of 0.5 to 16 mg/L). This may be explained by the fact that the observed CAZ-AVI MICs against *P. aeruginosa* were at least 4 times higher than the MICs against *Enterobacteriaceae*, and the CAZ-AVI dose used in this study was one-fourth of the proposed labeled dose. Based on the PK/PD target attainment analyses, > 90% of subjects are expected to achieve adequate exposure for *P. aeruginosa* isolates with MIC values ≤ 8 mg/L at the proposed labeled CAZ-AVI dose of 2.5 g. In addition, the imipenem dose of 0.5 g q6h may have been too low for infections due to *P. aeruginosa*, given that 1 g q8h or q6h is recommended for moderate to severe infections due to this pathogen (PRIMAXIN package insert, 2012). Although only 2 subjects infected by CAZ-NS *P. aeruginosa* isolates were identified from the Phase 2 studies (1 from cIAI, 1 from cUTI), CAZ-AVI was associated with clinical success in both subjects.

Finally, no formal inferential statistics were used to evaluate the efficacy of CAZ-AVI; instead, descriptive statistics were generated for the clinical studies of CAZ-AVI as part of a comprehensive evaluation of the totality of the data. However, these descriptive analyses of efficacy are appropriate in the context of the overall data package to support the initial approval of CAZ-AVI through the 505(b)(2) registration pathway, which is comprised of data on ceftazidime alone, avibactam alone, and CAZ-AVI. The data package provides extensive supportive evidence for clinical efficacy against the common Gram-negative pathogens causing serious bacterial infections, including MDR strains. The favorable microbiological and clinical outcomes associated with CAZ-AVI vs. CAZ-NS pathogens were numerically higher than those associated with comparator carbapenems. In addition, the effectiveness of the β-lactam in combination with a BLI model has been established among a number of approved agents (eg, piperacillin-tazobactam, amoxicillin-clavulanate, ticarcillin-clavulanate, ampicillin-sulbactam); therefore, knowledge of the effectiveness of ceftazidime and available BL-BLI agents helps mitigate the risk of the limited efficacy data associated with CAZ-AVI to date.

7.0 CONCLUSION

The available CAZ-AVI data meet the requirements of a 505(b)(2) NDA and is further supported by the unmet medical need for antimicrobial therapies effective against CAZ-NS pathogens. Serious infections such as cIAI and cUTI that are caused by MDR Gram-negative pathogens are increasing in incidence, and despite advances in medical care and antimicrobial therapy, remain important causes of mortality and prolonged hospitalization in the US. New antimicrobials with enhanced spectrum of activity are needed for such infections, especially given the rising incidence of highly-resistant and highly-virulent pathogens, such as CRE, ESBL-producing Gram-negative bacilli, and MDR *P. aeruginosa.*

The extensive data package, including the established efficacy of ceftazidime, in vitro evidence that avibactam extends the activity of ceftazidime vs. CAZ-NS isolates, PK/PD target attainment analyses, and data from in vivo animal models of infection, is predictive of the clinical efficacy of CAZ-AVI. Clinical efficacy data from the Phase 2 cIAI and ongoing Resistant Pathogen studies provide supportive evidence that CAZ-AVI administered at a dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h is effective for the treatment of infections caused by common Gram-negative pathogens—especially including CAZ-NS pathogens—and is a beneficial adjunct to the current armamentarium of parenteral antimicrobial therapy for serious and severe infections. Among subjects with cIAI or cUTI caused by CAZ-NS pathogens, favorable microbiological and clinical response rates were numerically higher in the CAZ-AVI group than in the comparator group (all of whom received carbapenem-based regimens). In addition to cIAI and cUTI, it is the Sponsor's opinion that the available evidence supports a favorable benefit-risk balance for the use of CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h in adults with infections caused by CAZ-NS Gram-negative pathogens in the face of limited or no other available therapeutic options.

Although the Phase 3 clinical development program is in progress, confidence of the efficacy of this 3rd-generation cephalosporin + BLI combination is bolstered by its inclusion of a well-known and established active component—ceftazidime has been used extensively over the last several decades as a safe and reliable Gram-negative-active β-lactam. In the context of major advances in PK/PD strategies, the combination of CAZ-AVI has been optimized to extend its activity against many contemporary resistant Gram-negative pathogens. PK/PD target attainment analyses predict that the clinical dosing regimen of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h infused over 2 h will provide adequate exposures to cover the most likely pathogens to be encountered among serious infections in the clinical setting based on analysis of extensive surveillance data. Furthermore, CAZ-AVI was well-tolerated with a similar adverse event profile to that of other systemic cephalosporins. Avibactam does not add alter the safety profile of ceftazidime based on the analysis of safety data.

The totality of the safety and efficacy data supports a positive benefit: risk balance for the use of CAZ-AVI in the current and future evolving environment of microbial resistance in serious infections caused by MDR Gram-negative pathogens. CAZ-AVI addresses distinct areas of unmet medical need and has the potential to provide a significant improvement in the treatment of cIAI and cUTI compared to marketed products, as evidenced by its in vitro and in vivo efficacy against CAZ-NS Gram-negative infections, with a safety profile consistent with that of ceftazidime and the cephalosporin class. CAZ-AVI also provides an option for the treatment of other infections due to MDR Gram-negative organisms in patients with limited or no other treatment options.

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